Feasibility, Safety, and Effectiveness of Psilocybin Therapy for Depression in Bipolar II Disorder

Protocol Number: IRB#20-32789

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Principal Investigator: Joshua Woolley, MD, PhD

Investigator-Initiated

IND#: 156218

Research Advisory Panel of California: PR#202115H

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the International Conference on Harmonisation Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All staff involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	**Feasibility, Safety, and Effectiveness of Psilocybin Therapy for Depression in Bipolar II Disorder**
Study Description:	This is an open-label, single-arm, pilot study of oral psilocybin treatment for depression in bipolar-II disorder (BD 2). The primary goal of this study is to examine the safety, tolerability, and feasibility of psilocybin therapy in this patient population. Fourteen participants, ages 18 to 70 with clinically diagnosed BD 2 with active depression (19+ on the Montgomery-Asberg Depression Rating Scale (MADRS)) in active outpatient mental health treatment in the community, and who meet all other inclusion and exclusion criteria at screening will be enrolled. Participants will complete preparatory visits with trained facilitators designed to provide information about the effects of psilocybin and to build rapport/trust. Following preparatory visits, participants will receive a low-moderate oral dose of 10mg psilocybin in a controlled environment, supervised by the facilitator(s) and a clinician who will conduct safety monitoring throughout. Participants will complete assessment and integration sessions with the facilitator(s) designed to help process the experience. Participants whose depression is remitted at 3 weeks post this initial 10mg dosage will be followed for the remainder of the study period but will not receive a second dose. Participants who tolerated the 10mg dosage well and whose depression has not remitted at 3 weeks post administration will complete a second psilocybin session. During the second session, participants will receive a moderate-high oral dose of 25mg psilocybin. The second psilocybin session will involve the same procedures and supervision as the first. Following psilocybin administration sessions, participants will again

complete integration sessions with the facilitator(s) designed to help process the experience. Primary outcome measures will assess safety, tolerability, and feasibility of study procedures. Efficacy will be measured by change in depression as measured by the MADRS three weeks after the final psilocybin administration.

Exploratory outcome measures will assess changes in sleep, quality of life, and therapeutic engagement.

Objectives:

Primary Objective: To examine the safety, tolerability, and feasibility of psilocybin treatment for depression in people with BD 2.

Exploratory Objective: To examine the potential efficacy of psilocybin treatment for improving clinically significant depression in people with BD 2.

Endpoints:

Safety and Tolerability Endpoints:

- Adverse Events (AEs): Incidence, severity, and frequency of Adverse Events (AEs) including Treatment-Emergent AEs (TEAEs) and Serious AEs (SAEs) will be measured before, during, and after each psilocybin administration session and at all follow-up evaluations. We will assess AEs via physical exams, vital sign monitoring, clinician-administered assessments, participant reports, facilitator reports, therapist reports, and support person reports.
- In terms of the following clinical assessments, an overall rating on the Clinical Global Impression-Improvement Scale (CGI-I; Guy, 2000) will serve as the summary of how the person is progressing in terms of safety, with a score of 6 or greater serving to indicate that the participant is worsening and should not progress with further dosing (if the participant has a dose remaining). The CGI-I will be administered at every in-person or assessment meeting.
- *For the following, change will be defined as differences between Initial Phone Screen (up to eight weeks prior to the first psilocybin administration session, Day A0), immediately prior to each psilocybin administration session (morning of Day A0, morning of Day B0) and four days following each psilocybin administration session (Day A4, A11, B4, and B11):*
    - Participant-reported manic and psychotic symptoms: Measured by the Altman Self-Rating Mania Scale (ASRM-14).
- *For the following, change will be defined as differences from Baseline (up to five weeks prior to the first psilocybin administration session, Day A0), to multiple timepoints Prep Visit 2 (up to seven days prior to the first psilocybin administration session, Day A0), the day after the first psilocybin administration session (Day A1), one week following the first*

psilocybin administration session (Day A7), two weeks following the first psilocybin administration session (Day A14), and three weeks following the first psilocybin administration session (Day A21). If the participant's depression remits at Day A21, participants will also be measured at follow up (Day A90). If a second dose of psilocybin is required (i.e., depression does not remit at A21), change will include differences one day after the first psilocybin administration session (Day B1), one week following the second psilocybin administration session (Day B7), two weeks following the second psilocybin administration session (Day B14), three weeks following the second psilocybin administration session (Day B21), and three months following the second psilocybin administration session (Day B90):

- Clinician-rated manic symptoms: Measured by the Young Mania Scale (YMS).
- Clinician-rated suicidality symptoms: Measured by the Columbia-Suicide Severity Rating Scale (C-SSRS).
- Clinician-rated psychotic symptoms: Measured by the positive subscale of the Positive and Negative Syndrome Scale (PANSS).

– *For the following, change will be defined as differences from Baseline (up to five weeks prior to the first psilocybin administration session, Day A0), one week following the first psilocybin administration session (Day A7), and three weeks following the psilocybin administration (A21). If the patient's depression remits at Day A21, this will also be assessed at three months after the first psilocybin session (Day A90). If a second psilocybin dose is required, participants will be assessed one week following the second psilocybin administration session (Day B7), three weeks following the second psilocybin administration session (Day B21), and three months following the second psilocybin administration session (Day B90):*

- Support person-reported outcomes: Measured by the Mood Disorder Burden Interview (MDBI)

– *For the following, change will be defined as differences from Baseline (up to five weeks prior to the first psilocybin administration session, Day A0), Day A21, and (if the patient's depression remits by Day A21) three months after the first psilocybin session (Day A90). If the patient's depression does not remit by Day A21, change will be between Baseline, Day B21 and three months after the second psilocybin session (Day B90):*

- Therapist-reported outcomes: Measured by modified PHQ-9 and modified ASRM-14

- Therapist-reported treatment engagement: Measured by the Engagement with Mental Health Services Scale (EMHSS)

Feasibility Endpoints:

- Participant recruitment rate: Feasibility of recruitment will be assessed as a percentage of participants who were contacted for pre-screening and consented.

- Participant retention rate: Retention feasibility will be assessed as a percentage of participants who began and completed treatment.

- Participant-reported acceptability of study procedures three months after the final psilocybin administration session (Day A90 or B90) depending on whether the patient remitted at Day A21: Measured by the study-specific Treatment Satisfaction Questionnaire - Participant (TSQ-P)

- Support person-reported acceptability of study procedures three months after the initial psilocybin administration (Day A90) if the patient remitted at Day A21 or three months following the second psilocybin administration session (Day B90) if the second dose was required: Measured by the study-specific Treatment Satisfaction Questionnaire - Support Person (TSQ-S).

Primary Efficacy Endpoint:

- *Change will be defined as the differences between Baseline (up to five weeks prior to the first psilocybin administration session, Day A0) and three weeks after the final psilocybin administration session (either A21 or B21):*

    - Clinician-rated depressive symptoms: Measured by the Montgomery-Asberg Depression Rating Scale (MADRS)

Secondary Efficacy Endpoints:

- *For the following, change will be defined as the difference between Baseline (up to five weeks prior to the first psilocybin administration session, Day A0) and one and two weeks after the first psilocybin administration session (Day A7 and Day A14). If the participant remits at Day A21, change will also include differences from Baseline to three months after the first psilocybin administration session (Day A90). If a second dose of psilocybin is required, change will include differences from Baseline to one and two weeks after the second psilocybin session (Day B7 and Day B14), and three months after the second psilocybin session (B90):*

- Clinician-reported depressive symptoms: Measured by the Montgomery-Asberg Depression Rating Scale (MADRS)

– *For the following, change will be defined as the differences between Initial Phone Screen (up to eight weeks prior to the first psilocybin administration session, Day A0), Prep Visit 1 (up to three weeks prior to the first psilocybin administration session, Day A0), immediately prior to the first psilocybin administration session (morning of Day A0), and four days, eleven days and three months after the first psilocybin session (Day A4, A11, and A90). If a second dose of psilocybin is required, change will include differences immediately prior to the second psilocybin administration session (morning of Day B0), four days, eleven days and three months after the second psilocybin session (Day B4, B11, and B90):*

- Participant-reported depressive symptoms: Measured by the Quick Inventory of Depressive Symptomatology (QIDS-SR).

– *For the following, change will be defined as the differences between Baseline (up to five weeks prior to the first psilocybin administration session, Day A0), Prep Visit 2 (up to one week prior to the first psilocybin administration session, Day A0), immediately prior to the first psilocybin administration session (morning of Day A0), one week and two weeks after the first psilocybin administration session (Day A7 and Day A14) and three weeks after the first psilocybin administration session (Day A21). If the participant remits at Day A21, change will include differences three months after the first psilocybin session (Day A90). If a second psilocybin dose is required, change will include differences immediately prior to the second psilocybin administration session (morning of Day B0), one and two weeks after the second psilocybin administration session (Day B7 and B14), three weeks after the second psilocybin session (Day B21), and three months after the second psilocybin session (Day B90):*

- Participant-reported sleep quality: Measured by Insomnia Severity Index (ISI).

– *For the following, change will be defined as the differences between Baseline (up to five weeks prior to the first psilocybin administration session, Day A0), three weeks after the first psilocybin session (A21), and three months after the second psilocybin session (Day A90) if the patient remits at Day A21. If a second psilocybin dose is required, change will be defined as the differences between Baseline (up to five weeks prior to the first psilocybin administration session, Day A0), three weeks after the second psilocybin session (Day B21), and three months after the second psilocybin session (Day B90):*

- Quality of Life-Bipolar Disorder: Measured by the Quality of Life in Bipolar Disorder Questionnaire (QoL-BD full scale)

- Participant-reported change in adult attachment: Measured by the 16 item Experiences in Close Relationships-Modified 16-Item Scale (ECR-M16)

- Bipolar Disorder recovery: Measured by the Bipolar Recovery Questionnaire (BRQ)

– *For the following, change will be defined as the differences between Baseline (up to five weeks prior to the first psilocybin administration session, Day A0) and three months after the first psilocybin session (Day A90) if the participant remits at Day A21. If the second dose is required, the participant will complete this at Baseline and three months after the second psilocybin session (Day B90):*

- Participant-reported personality disorder symptoms: Measured by the Personality Inventory for DSM-5

- Clinician-reported borderline personality disorder symptoms: Measured by the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD).

- Participant-reported trauma-related symptoms: Measured by the PTSD Checklist for DSM-5 (PCL-5)

– *We will use six additional measures to quantify subjective effects of psilocybin:*

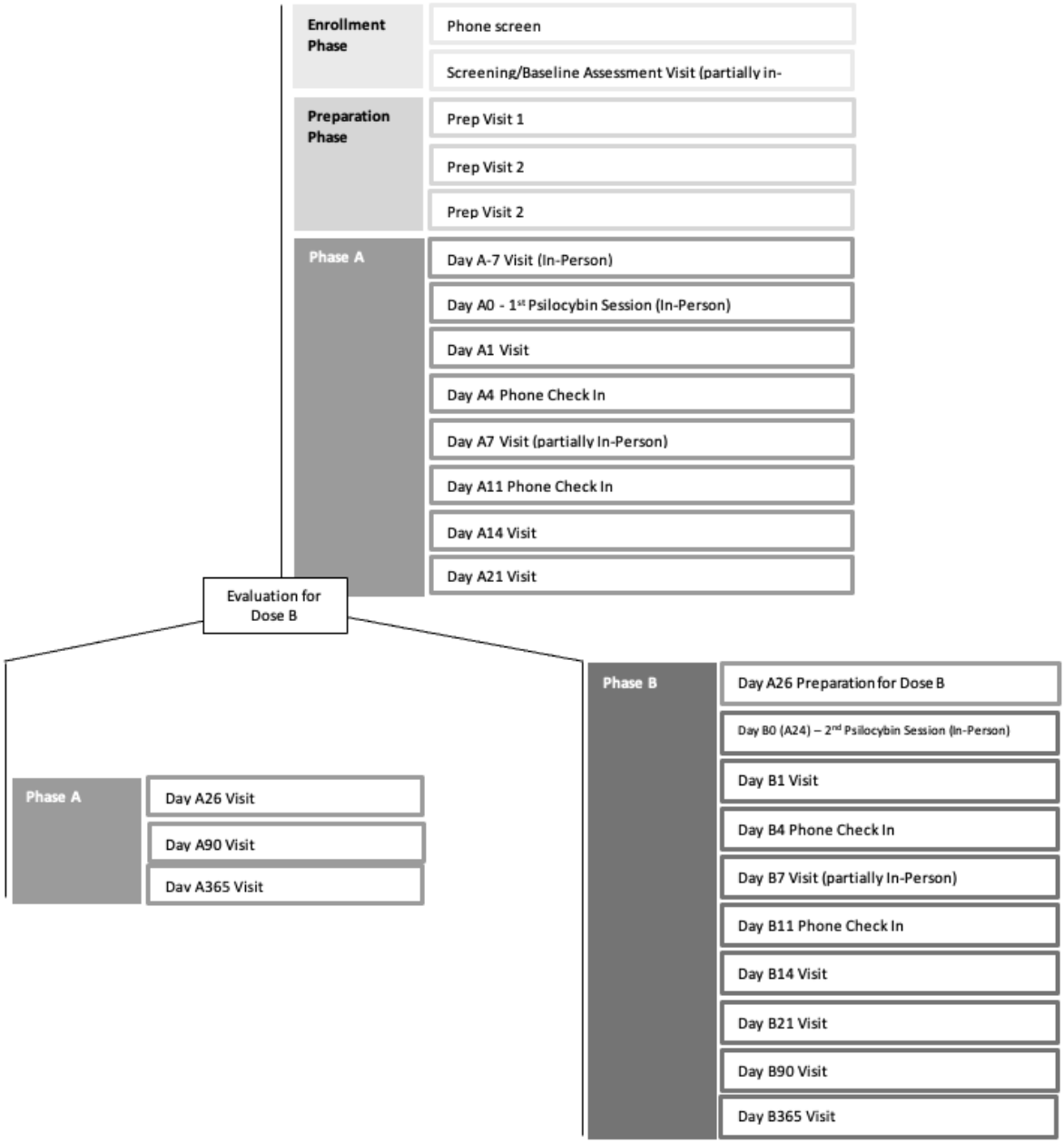
- Subjective psychedelic intensity ratings will be measured using the Likert scale (0-10 rating scale, 0=not intense at all, 10= highest intensity imaginable), along with facilitator perceived rating of drug intensity, at 30, 60, 90, 120,240, and 360 thereafter
- Participant-reported acute psilocybin effects: Measured by the Mystical Experiences Questionnaire (MEQ30), the Challenging Experiences Questionnaire (CEQ), Emotional Breakthrough Inventory (EBI), Post-dose journal, and the Psychological Insight Questionnaire (PIQ).) at the end of each psilocybin administration session (Day A0 and Day B0).

- Participant-reported long-term psilocybin effects: Measured by the study-specific Transformational Experiences Questionnaire (TEQ) three weeks after the initial psilocybin session (A21) if the participant remitted at Day A21, or after three weeks (Day B21) if the second psilocybin dose was required.

- An Oura ring will be worn by participants to track measures related to heart rate and body temperature.

Study Population:	Fourteen people with BD 2 ages 30-65 with moderate to severe depression.
Phase:	Phase 2a
Description of Sites/Facilities Enrolling Participants:	This is a single-site study; all procedures will be completed at the University of California San Francisco (UCSF).
Description of Study Intervention:	Psilocybin 3-[2-(dimethylamino)ethyl]-1H-indol-4-yl] dihydrogen phosphate will be administered one or two times. If two doses are administered, this will occur, during two separate sessions separated by at least 3 weeks. Participants will receive a test dose of 10mg orally during the first session and a second dose of 25mg orally at the second session if their depression has not remitted at 3 weeks post first dose.
Study Duration:	24 months.
Participant Duration:	4-6 months.

1.2 SCHEMA



See **Section 1.3 Schedule of Activities** for specific examinations, assays, and assessments conducted at each timepoint.

1.3 SCHEDULE OF ACTIVITIES

Table 1. Schedule of Activities

	Enrollment Phase		Preparation Phase[2]				Phase A									Phase B								
Visit/Contact:	Phone screen	Screening /Baseline Visits	Prep 1 Visit	Prep 2 Visit	Prep 3 Visit	Day A-7 Visit	Day A0 Visit	Day A1 Visit	Day A4 Phone	Day A7 Visit	Day A11 Phone	Day A14 Visit	Day A21 Visit	Day A26 Visit[4]	Day A90 Visit	Day B0 Visit	Day B1 Visit	Day B4 Phone	Day B7 Visit	Day B11 Phone	Day B14 Visit	Day B21 Visit	Day B90 Visit	Optional A/B365 Visit
Study Procedures:																								
Phone Screen	✓																							
Informed Consent		✓																						
Psychiatric History (SCID)		✓																						
QIDS-SR	✓	✓		✓	✓		✓		✓		✓		✓		✓	✓		✓		✓		✓	✓	
Medical History	✓	✓																						
Physical exam + blood tests		✓																						
Medication review		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Family History		✓																						
Pregnancy Test + Substance Screen (UDS)		✓					✓									✓								
Breathalyzer							✓									✓								
MADRS		✓		✓						✓		✓	✓		✓				✓		✓	✓	✓	✓
YMRS		✓		✓				✓		✓		✓	✓		✓		✓		✓		✓	✓	✓	✓
C-SSRS		✓		✓				✓		✓		✓	✓		✓		✓		✓		✓	✓	✓	✓
PANSS - positive symptoms		✓		✓				✓		✓		✓	✓		✓		✓		✓		✓	✓	✓	✓
ASRM-14-SR	✓						✓		✓		✓					✓		✓		✓				
ISI		✓		✓	✓		✓			✓		✓	✓		✓	✓			✓		✓	✓	✓	✓
Treatment Expectancy (SETS)		✓																						
QoL-BD		✓											✓		✓							✓	✓	✓
PCL-5		✓													✓								✓	✓
ACE		✓																						
ZAN-BPD		✓													✓								✓	✓

***Therapist Assessments**		✓											✓		✓							✓	✓	
***Support Person Assessments**		✓								✓			✓		✓				✓			✓	✓	
Psilocybin Prep			✓	✓	✓									✓										
Psilocybin Integration								✓		✓		✓		✓			✓		✓		✓	✓		
Intensity Rating							✓									✓								
MEQ-30							✓									✓								
CEQ							✓									✓								
PIQ							✓									✓								
EBI							✓									✓								
Post-Dose Journal							✓									✓								
TEQ													✓									✓		
ECR-M16		✓											✓		✓							✓	✓	✓
TSQ-P															✓								✓	
***Support Person Assessments**															✓								✓	
Qualitative Interview															✓								✓	
Phone Check-In									✓		✓							✓		✓				
AE Monitoring		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	
BRQ		✓											✓		✓							✓	✓	✓
DESS		✓					✓									✓								
CGI-I		✓	✓	✓	✓		✓	✓		✓		✓		✓	✓	✓	✓		✓		✓	✓	✓	✓
Computer Tasks		✓		✓		✓				✓									✓					

[1] In addition to vital signs taken at the start of the Day A0 and Day B0 visits, heart rate and blood pressure are taken periodically during the period of acute psilocybin effects on each day.

[2] At the discretion of the investigators, additional Prep Visits can be scheduled if thought to be important for maximizing participant safety and well-being. Participants will also have the option to complete 2-3hour Prep Visits, instead of 3-2hour Prep Visits - total time spent in Prep will be the same in either case.

[3] The primary goal of the Phone Check-ins are to ensure participant safety. Each contact will last approximately 5-15 minutes, but could be longer to address participant concerns and to adequately assess clinical status if concerns arise. At the discretion of the investigators, additional phone contacts can be scheduled if thought to be important for maximizing participant safety and well-being.

[4] This visit will serve as an integration and closure visit for A0 dose administration or the preparation visit for B0 dose administration depending on if the participant is continuing on to B0 dose as determined by the A21 assessments.

[5] Participant's vitals will be taken to both acclimate participant to this process for dosing session and ensure new development of hypertension has not occurred.

[6] Participants may be asked to complete 2-minute video diary entries 1-5 times per week

2 INTRODUCTION

2.1 STUDY RATIONALE

Bipolar II disorder (BD 2) is a debilitating illness that affects 0.4% of the world's population irrespective of nationality, ethnic origin, or socioeconomic status. It is a leading cause of disability especially among young people (Grande et al., 2016), and is best conceived as a subgroup of bipolar disorders with a specific longitudinal pattern of illness severity, including lifetime number of mood episodes, suicide risk, and treatment response. BD 2 is associated with higher rates of unfavorable illness characteristics compared to Bipolar I disorder (BD 1; Dell'Osso et al., 2015), including more depressive (Endicott et al., 1985; Judd, Akiskal, et al., 2003; Judd, Schettler, et al., 2003) and overall episodes (Goodwin et al., 2007), and higher rates of anxiety disorder comorbidity (Henry et al., 2003; Zoltán Rihmer et al., 2001), rapid cycling course (Baldessarini et al., 2000; Kupka et al., 2003), and possibly greater risk of suicide attempts (Baek et al., 2011; Dunner et al., 1976; Merikangas et al., 2011; Novick et al., 2010; Zoltan Rihmer & Pestality, 1999; Valtonen et al., 2005). The more frequent and longer lasting depressive episodes and sub-syndromal depressive symptoms in BD 2 are particularly impairing impacting functioning, psychosocial disability, and risk for suicide attempts (Pallaskorpi et al., 2017), all of which are directly linked with increasing percentages of depressive symptoms (Hadjipavlou et al., 2012). Indeed, in bipolar illnesses, depressive symptoms are more disabling than hypomanic symptoms and are potentially as disabling as, or more disabling than mania symptoms (Ruggero et al., 2007). Despite their clinical importance, currently available treatment approaches for depression in BD 2 are inadequate. Pharmacotherapies such as lithium and antipsychotics can sometimes be effective but are associated with significant side effects (Post, 2016; Szmulewicz et al., 2017). Even with treatment, many patients do not adequately respond and do not regain full functioning, especially in the social realm (Wingo et al., 2010). Thus, novel therapeutic approaches for depressive symptoms in BD 2 are desperately needed. Though recent studies suggest that a single dose of psilocybin produces significant and sustained improvement in depressive symptoms (e.g., Carhart-Harris et al., 2016; Griffiths et al., 2016; Ross et al., 2016) and in treatment resistant depression (Carhart-Harris et al., 2018; Carhart-Harris et al., 2016), psilocybin has not been tested in people with bipolar disorder. Given that novel pharmacological agents are urgently needed to treat debilitating depressive episodes in BD 2, it is important to assess the safety and feasibility of administering psilocybin in this clinical population.

2.2 BACKGROUND

2.2.1 INTRODUCTION TO PSILOCYBIN

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is a tryptamine serotonergic psychedelic that can induce an acute altered state of consciousness characterized by changes in affect, sensory perception, cognition, and sense of self (Dos Santos et al., 2020). Like other tryptamines, it shares its core structure with the neurotransmitter serotonin (5-hydroxytryptamine [5-HT]) and modulates multiple targets, including 5-HT receptor subtypes, monoamine transporters, and trace-amine-associated receptors (Rickli et al., 2016).

Psilocybin is found in several species of hallucinogenic mushrooms and has been used as part of ritual, religious, and healing practices by indigenous peoples for thousands of years (Hofmann, 2009). It was synthesized in the laboratory for the first time in 1958 (Passie et al., 2002) and marketed by Sandoz (as Indocybin) in the 1960s. Despite a favorable tolerability profile and preliminary evidence of benefit in humans, concern about the general public's use of psychedelics precipitated legislation that limited clinical research using psilocybin and similar drugs.

In 1970, the Controlled Substances Act of the Comprehensive Drug Abuse Prevention and Control Act effectively halted psychedelic studies in humans (Reiff et al., 2020).

Contrary to the politicized view of psychedelics after the 1960s, subjective (Carhart-Harris & Nutt, 2010; van Amsterdam et al., 2011), observational (Bouso et al., 2012), and epidemiological data (Hendricks et al., 2015) suggest that use of these drugs presents a lower risk of harm than other commonly available substances such as alcohol and tobacco and may even be associated with mental health benefits. In an analysis of 110 healthy participants who completed a total of 227 psilocybin administration sessions, there were no instances of prolonged psychosis, persisting perceptual changes, or any other long-term functional impairment in any participants (Studerus et al., 2011). Despite its potentially dramatic effects on consciousness, psilocybin is not associated with cognitive impairment or delirium even at high dosages (Barrett et al., 2018), and may actually promote neuroplasticity (Ly et al., 2018). These lines of evidence have led to renewed interest in research to evaluate psilocybin's clinical utility. The fact that novel pharmacologic treatments for neuropsychiatric disorders are lacking, and many pharmaceutical companies have decreased research on brain targets (Al-harbi, 2012; Nutt et al., 2020) has also contributed to the resurgence of psychedelic research. Revisiting drugs that fell out of favor before rigorous testing could be conducted seems all the more critical.

Over the past fifteen years, a series of studies has generated preliminary evidence that psilocybin treatment may improve depression and anxiety in people with life-threatening cancer (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016), obsessive-compulsive symptoms (Moreno et al., 2006), treatment-resistant depression (Carhart-Harris et al., 2016), tobacco abuse (Johnson et al., 2014), and demoralization in long-term AIDS survivors (Anderson et al., 2020). Though acute psychedelic effects of the drug resolve within four to five hours of oral administration, psilocybin's beneficial effects on mood and well-being appear to persist for weeks to months (Griffiths et al., 2016). In addition, these recent studies suggest a high level of safety and tolerability. These promising findings have led to the expansion of psilocybin research for treating mood disorders as well as for other disorder including migraine headache (NCT03341689), cluster headache (NCT04280055), anorexia nervosa (NCT04052568), mild cognitive impairment/early Alzheimer's Disease (NCT04123314), and opioid use disorder (NCT04161066). Though the extant literature is limited by small sample sizes and there are challenges to developing psychedelic treatments (Sellers & Leiderman, 2018), positive results observed thus far clearly support continued investigation of psilocybin's potential as a therapeutic.

2.2.2 PHARMACOLOGY OF PSILOCYBIN AND POTENTIAL MECHANISMS OF ACTION

After oral ingestion, psilocybin is dephosphorylated by hepatic first pass metabolism to its active metabolite, psilocin (4-N,N-dimethyltryptamine). Psilocin is a serotonin transporter inhibitor and 5-HT2A receptor partial agonist with <40% activation efficacy that also binds to the 5-HT2C, 5-HT1A, and 5-HT1B receptors (binding affinities in descending order) (Johnson et al., 2019; Rickli et al., 2016). When taken orally, psilocybin has approximately 50% bioavailability. It has no known P450 interactions and is instead glucoronidated and renally excreted (Hasler et al., 2002; Passie et al., 2002). Psilocin is detectable in plasma 20 minutes following ingestion of the parent compound (Brown et al., 2017; Hasler et al., 1997) and has a half-life of two to three hours. Subjective effects begin within one hour of administration, peak at approximately two hours, and dissipate by approximately six hours. The subjective effects of psilocybin are dose-dependent and context-dependent—they may range from blissful mystical-type experiences, euphoria, and pleasurable perceptual changes (e.g., synesthesia, sensory illusions, auditory and visual hallucinations) to unpleasant experiences of anxiety, negative emotional states, and psychotic-like effects such as depersonalization and derealization (Dinis-Oliveira, 2017; Nicholas et al., 2018; Passie

et al., 2002). Additional information regarding the pharmacology and toxicology of psilocybin can be found in the Investigator's Brochure (IB).

Both preclinical and human studies indicate that agonism at cortical 5-HT2A receptors (Madsen et al., 2019; D. E. Nichols, 2016) is crucial for psilocybin's characteristic effects (dos Santos et al., 2016). For example, administration of a 5-HT2A antagonist reduces or blocks both the subjective and neurophysiological effects of serotonergic psychedelics (Preller et al., 2017; Vollenweider et al., 1997), and 5-HT2A receptor occupancy correlates with the intensity of a psychedelic experience (Madsen et al., 2019). The 5-HT2A receptor is densely expressed in the cerebral cortex, localized on the cell bodies and apical dendrites of pyramidal neurons. They are also found on GABAergic interneurons that modulate pyramidal cell firing (Andrade, 2011). 5-HT2A receptor activation leads to dysregulation of spontaneous activity in cortical cells, which has provided support for the hypothesis that psychedelics exert their effects primarily by un-weighting predictive models encoded in the brain (Carhart-Harris & Friston, 2019). A variety of imaging studies offer support for this idea, showing that psilocybin produces marked alterations in brain network connectivity during the time of drug action, enabling a less constrained cognitive state (C. D. Nichols & Hendricks, 2020). Thus, psilocybin may reduce the stability and integrity of established neural networks while simultaneously increasing connectivity between networks. These acute changes may effectively open a therapeutic window that facilitates insight and emotional breakthrough (Roseman et al., 2019). Findings that a sense of emotional breakthrough during the period of acute psilocybin effects correlates with long-term benefits offers additional support for this hypothesis (Aday et al., 2020).

How these 5-HT2A receptor-mediated changes relate to longer term therapeutic benefits of psychedelics remain to be determined, and much remains to be understood about psilocybin's effects. Evidence that the drug is a potent modulator of glutaminergic activity in prefrontal circuits (Mason et al., 2020; Vollenweider & Kometer, 2010) and that psychedelics may promote plasticity in neural circuits relevant to neuropsychiatric symptoms (Ly et al., 2018) offer clues but require further elucidation. Evidence from animal studies also suggests that the anti-inflammatory effects of 5-HT2A receptor activation may play an important role in its therapeutic effects (Flanagan & Nichols, 2018). Finally, the role of the psychotherapeutic guidance that is a cornerstone of modern clinical trials of psilocybin is unclear—whether this component is necessary to harness the drug's effects will require careful evaluation (Johnson et al., 2008; Roseman et al., 2018).

Though additional study is needed to clarify the mechanisms by which serotonergic psychedelics produce changes in affect, cognition, and outlook, these lines of evidence suggest that psilocybin treatment is a markedly different approach to improving neuropsychiatric symptoms.

2.2.3 CLINICAL PSILOCYBIN STUDIES

Though numerous studies of psychedelic effects in humans were conducted between the 1950s and 1970, dubbed the "pre-prohibition era" (Dos Santos et al., 2020; Rucker et al., 2018), most do not meet current methodological standards (Bogenschutz & Ross, 2016; dos Santos et al., 2016; Johnson et al., 2008). Here we will review only those recent clinical studies that have used rigorous experimental designs and a more targeted or objective approach to outcomes:

2.2.3.1 PSILOCYBIN EFFECTS ON ANXIETY AND DEPRESSION

Three double-blind, randomized controlled trials have examined the impact of psilocybin on depressive and anxious symptoms in patients with life-threatening cancer diagnoses (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). Grob et al. (2011) conducted a double-blind, randomized crossover clinical trial examining the effects

of psilocybin in participants (N=12) with advanced-stage cancer and a DSM-IV diagnosis of acute stress disorder, generalized anxiety disorder, anxiety disorder due to cancer, or adjustment disorder with anxiety. Each participant completed two psilocybin treatment sessions in random order, several weeks apart. Participants received (14 mg/70 kg) during one session and an active placebo (250 mg niacin) during the other. State-Trait Anxiety Inventory (STAI) trait scores (but not state scores) were significantly decreased at one month and at three months following the second psilocybin session. Though Beck Depression Inventory (BDI) scores did not change between baseline and follow-up at two weeks, they were significantly lower at both the one month and the six-month follow-up time points.

Ross et al. (2016) conducted a similar double-blind, randomized crossover trial testing psilocybin for patients (N=29) with cancer-related anxious and depressive symptoms. Participants completed two medication sessions spaced several weeks apart: psilocybin (21 mg/70 kg) and placebo (250 mg niacin). Anxious symptoms measured by the Hospital Anxiety Scale (HADS-A) and STAI and depressive symptoms measured by the Hospital Depression Scale (HADS-D) and Beck Depression Inventory (BDI) were significantly reduced following the psilocybin sessions. These improvements persisted to the final study time point 26 weeks following the second session.

Another similar but larger double-blind randomized crossover trial investigating the effects of psilocybin in patients (N=51) with terminal cancer and a DSM-IV diagnosis of an anxious or depressive disorder was conducted by Griffiths et al. (2016). Participants received a moderate-high dose of psilocybin (22 mg/70 kg) during one session and a low dose (1 mg or 3mg/70 kg), designed to serve as an active control, during the other several weeks later. The moderate-high dose, but not the low dose, was associated with significant and substantial decreases in depressive and anxious symptoms after five weeks as measured by the HAM-D (Cohen's d=1.33) and the HAM-A (Cohen's d=1.1), respectively. The six-month response rate (defined as a decrease of >/=50% in HAM-D or HAM-A scores) was 78% for depressive disorders and 83% for anxiety disorders and effect sizes were notably larger relative to baseline (d=2.98 and d=2.40, respectively). At the six-month follow-up timepoint, over 80% of participants reported that the psilocybin experience changed their sense of well-being or life satisfaction moderately or very much. Importantly, two-thirds reported that it was one of the top five most meaningful experiences of their lives.

Carhart-Harris et al. (2016) conducted an open-label feasibility trial (N=12) of psilocybin for a different clinical population: patients with moderate to severe treatment-resistant depression (TRD). Participants received two oral doses of psilocybin in association with psychological support: 10 mg during the first session and 25 mg during the second session seven days later. Depressive symptoms measured by the Quick Inventory of Depressive Symptomatology (QIDS) decreased significantly and markedly from baseline to one week (Hedges' g=3.1) and from baseline to three months (Hedges' g=2). Secondary measures of depression (the HAM-D and the BDI) also reflected significant improvements in symptomatology. Post-treatment, participants also became significantly more accurate at predicting the occurrence of life events, suggesting that psilocybin treatment might ameliorate pessimism bias associated with treatment-resistant depression (Lyons & Carhart-Harris, 2018).

Together, these four studies provide preliminary evidence of psilocybin's ability to treat depression and anxiety. A recent systematic review (Muttoni et al., 2019) and a meta-analysis (Romeo et al., 2020) of psychedelic therapies for mood symptoms found evidence of potential efficacy, and large multicenter efficacy trials are currently planned or underway (ClinicalTrials.gov Identifier: NCT03181529, NCT03380442, NCT03429075). Psilocybin's designation as a Breakthrough Therapy for depression by the Food and Drug Administration (FDA) (Reiff et al., 2020), also reflects growing support for continued investigation of the drug's clinical potential.

2.2.3.2 PSILOCYBIN EFFECTS ON OTHER DISORDERS

There is preliminary evidence that psilocybin may offer benefit for other clinical populations. An open-label study of psilocybin-assisted group therapy for long-term AIDS survivors (N=18) completed by our research group demonstrated substantial improvements in demoralization (Cohen's d=1.02) and symptoms of post-traumatic stress disorder (d=0.78)(Anderson et al., 2020). Moreno et al. (2006) assessed the effects of four single-dose exposures to psilocybin in participants (N=9) with obsessive-compulsive disorder (OCD) at doses ranging from subhallucinogenic (1.75 mg/70 kg) to frankly hallucinogenic (21 mg/70 kg). Psilocybin sessions were separated by at least one week. OCD symptoms as measured by the Yale-Brown Obsessive Compulsive Scale (YBOCS; Goodman et al., 1989) acutely decreased in all participants during the psilocybin sessions and effects generally lasted beyond the 24-hour follow-up time point. Interestingly, the authors found no significant effect of dose. A randomized controlled parallel-group study in patients with OCD that aims to expand on these findings is currently underway (NCT03300947).

Two other open-label studies have examined psilocybin's effects on substance use disorders. Johnson et al. (2014) included two to three psilocybin sessions (20mg/70 kg, then 30 mg/70 kg) during a fifteen-week course of cognitive behavioral therapy for participants (N=15) who wanted to quit smoking. Twelve of the participants (80%) were abstinent 6 months following treatment and nine (75%) at two and a half years. Bogenschutz et al. (2015) conducted an open label study of psilocybin-assisted motivational enhancement therapy for participants (N=10) with alcohol use disorder. Participants received two doses of psilocybin (14 mg/70 kg, then 21 mg/70 kg) several weeks apart. Self-reported abstinence was significantly increased at four and 36 weeks following treatment. These authors and other research groups are conducting additional trials to replicate and extend these findings in patients with alcohol (NCT02061293), nicotine (NCT0194399), and cocaine (NCT02037126) use disorders.

2.2.3.3 SAFETY AND TOLERABILITY OF PSILOCYBIN IN CLINICAL TRIALS

Since clinical research with psilocybin resumed in the early 1990s, there have been no reports of serious adverse events (Bogenschutz & Ross, 2016; dos Santos et al., 2016; Studerus et al., 2011) and no cases of prolonged psychotic reactions in any trial (dos Santos et al., 2016). The most common adverse effects observed are transient nausea, headache, and anxiety; psilocybin is also associated with acute increases in heart rate and blood pressure that appear to resolve spontaneously. No pharmacologic interventions have been required to address any of these adverse effects in clinical trials conducted over the last three decades (Muttoni et al., 2019; Romeo et al., 2020). Furthermore, it is important to note that evidence from animal and human studies indicate that serotonergic psychedelics like psilocybin are not habit-forming (Bogenschutz & Johnson, 2016; Carhart-Harris & Nutt, 2013), and tend to be associated with sporadic use patterns (D. E. Nichols, 2004).

However, pre-prohibition era studies provide evidence of the potential risks associated with psychedelic treatment. While psychedelic use is not associated with deterioration of mental health, those with underlying vulnerabilities to psychosis could experience an exacerbation of these symptoms (Rucker et al., 2018). The practice of carefully screening participants is likely an important contributor to psilocybin's excellent safety and tolerability profile in the modern era (Johnson et al., 2008). Context is also widely believed to be a critical component of the positive effects observed in recent clinical trials (Carhart-Harris, Roseman, et al., 2018). Pre-prohibition era studies that administered psilocybin without significant preparation and guidance outside of supportive settings revealed that a wide range of responses to the drug were possible, including panic and potentially dangerous behaviors (Johnson et al., 2008; Reiff et al., 2020). Neglecting the importance of context may have precipitated these adverse effects and thus contributed to historical negative stigma associated with psychedelics (Lee & Shlain, 1992).

Modern psilocybin trials reflect an appreciation for optimizing the conditions under which the drug is administered both to reduce risk of adverse events and to increase the likelihood that participants will experience lasting

positive emotional and behavioral changes (Johnson et al., 2008). All of the clinical trials reviewed here included procedures that explicitly address the mindset of participants just prior to psilocybin exposure, the setting in which dosing occurs, and processing of the experience following psilocybin exposure. Sufficient preparation for the psychedelic experience, rapport-building with the study staff, attention to details of the physical space to enhance comfort and safety, and post-drug session meetings to discuss the experience are now considered essential best practices for psychedelic research (Bogenschutz & Ross, 2016; Johnson et al., 2008).

2.2.4 Depression in Bipolar 2 Disorder

While bipolar disorders have been broadly portrayed as a spectrum of mood fluctuations (e.g., Akiskal & Mallya, 1987; Merikangas et al., 2007, 2011), the original conceptualization of BD 2 (as distinct from BD 1) was understood as a milder form of the illness. This is likely due to the fact that the main diagnostic criteria that differentiates BD 1 and BD 2 is the absence of a manic episode in BD 2; instead BD 2 requires no severe impairment, but instead 'hypomania'. However, in the last few decades, research has indicated that BD 2 has shown to be functionally *more* severe in several ways than BD 1, especially in terms of depressive episodes. For example, in one study of over 500 outpatients with BD 1 or 2, individuals with BD 2 were more likely to have current depression, more severe depressive episodes, a first-degree relative with a mood disorder, an earlier age of onset, more personality disorder diagnoses, and be more rapid cycling than individuals with BD 1 (Dell'Osso et al., 2015). Notably for the present study these researchers found that individuals with BD 2 were significantly less likely to have had experiences of prior psychosis, or psychiatric hospitalizations. Several other studies have shown very similar differences in BD 2 versus BD 1, with BD 2 individuals showing more depressive episodes (Endicott et al., 1985; Judd, Akiskal, et al., 2003) more overall mood episodes (e.g., Goodwin et al., 2007; Vieta et al., 1997), more rapid cycling of mood (e.g., (Benazzi, 2004) and some studies indicating higher risk of suicide (e.g., Baek et al., 2011; Zoltan Rihmer & Pestality, 1999; but see Merikangas et al., 2011; Novick et al., 2010). There is also evidence that individuals with BD 2 have a more delayed diagnosis, a longer latency before treatment, and fewer treatment options (e.g., Altamura et al., 2010; Coryell et al., 1985).

Given the higher frequency and length of depressive and mood episodes, the delayed diagnosis and limited treatment options, researchers have noted that BD 2 is an especially challenging disorder (Altamura et al., 2010; Dell'Osso et al., 2015). For one, prescribers are often hesitant to prescribe antidepressants for fear of activating a manic episode (e.g., Coryell et al., 1985; Endicott et al., 1985), and psychosocial treatments of bipolar disorder are currently limited (e.g., (Wingo et al., 2010). Thus, novel treatments, especially of depressive symptoms in BD 2 are desperately needed.

2.2.5 Potential benefits of psilocybin treatment in Bipolar 2 Disorder

Psilocybin treatment may offer a promising and fundamentally different approach to improving depression in BD 2. It is important to investigate as one or two doses of psilocybin may produce rapid, sustained antidepressant effects that could decrease symptoms and increase quality of life for people with BD 2 while minimizing polypharmacy.

For those who respond to SSRIs and similar agents that are the mainstays of pharmacologic treatment for depression and anxiety, improvement generally requires several weeks of daily drug administration (Rush et al., 2006). SSRI treatment of bipolar patients remains controversial, with evidence both for short-term efficacy but also the potential for harm. For BD 1 patients, it is believed that the greatest risk is for the iatrogenic induction of mania with antidepressants. For BD 2 patients there is some evidence that SSRI's may improve mood in the short term. However, not only is this improvement not typically as sustained as that seen on lithium, the day-to-day

course of BD 2 treated with antidepressants may be more unstable with mixed and rapid-cycling episodes (J. D. Amsterdam & Shults, 2010). All of this has led some experts to argue against SSRI use in BD 2 (Goodwin & Ghaemi, 2003). Further, despite advances in the tolerability of antidepressant/antianxiety medications, these agents continue to be associated with a significant short- and long-term side effect burden that impacts patients' treatment adherence (Cassano & Fava, 2004; Kelly et al., 2008), and side effects often precipitate premature discontinuation or the use of subtherapeutic doses (Demyttenaere et al., 2001; Hu et al., 2004). Given the limited medication options for people with BD 2, novel treatments are important to consider. In previous clinical trials, psilocybin treatment has produced rapid reductions in depressive symptoms after only one or two exposures to the drug. Shortening time to improve symptoms while also reducing risks associated with rapid-cycling mood episodes could benefit patients with BD 2 substantially.

A recent systematic review of 34 studies of the longer-term effects of serotonergic psychedelics found evidence that improvements in depression, anxiety, well-being, and attitudes may persist for several months following drug administration (Aday et al., 2020). These enduring benefits may reflect psilocybin-induced changes in the underlying neural correlates of affect. Barrett et al. (2020), for example, found that while some changes in affect were observed one week after psilocybin returned to baseline after one month, positive affect remained elevated and anxiety reduced at one month. Furthermore, psilocybin-induced increases in functional connectivity across brain networks were sustained after one month. Findings from additional neuroimaging studies as well as the results of recent clinical trials have led some researchers to hypothesize that serotonergic psychedelics may directly access and remedy underlying causes of mood symptoms (Nutt et al., 2020).

Importantly, all modern clinical trials have excluded individuals with bipolar disorder, and in most studies, researchers excluded all individuals with a family history of bipolar disorder, in order to minimize the risk of initiating a manic episode (e.g., Studerus et al., 2011). In spite of the caution of researchers of activating a manic episodes, there are no reported cases (in this screened population) of mania beyond the initial common euphoric effects of the drug onset and the 'afterglow' of the effects approximately 24 hours after (e.g., Rucker et al., 2018; Studerus et al., 2011). In terms of recreational hallucinogen use in the general population, results from a large-scale survey of more than 130,000 participants (which likely included individuals with bipolar disorder or a family history of bipolar disorder), indicated that hallucinogen use was not a predictor for subsequent mania or psychosis (Johansen & Krebs, 2015). In another study of over 1900 participants in a community sample that reported using psilocybin and other hallucinogens, there were no clear reports of enduring symptoms of mania, or activated bipolar illness (Carbonaro et al., 2016). In historical studies and case reports, the adverse events that appear to describe mania exists primarily in a few studies on LSD in the 1950s (Rucker et al., 2018). Additionally the only LSD study that appears to describe manic symptoms specifically is one of the earliest research studies of LSD, which focused on individuals with schizophrenia and individuals with 'chronic mania' and 'manic depression' (Busch & Johnson, 1950). In those individuals with mania/manic depression the authors noted an increase in irritability and agitation, but these experiences appeared to be responses to the drugs and not long-term effects per se. That is, participants did not appear to be followed up with after the study was completed. Perhaps the strongest evidence for the activation of mania are case reports of recreational and community guided use of LSD, ayahuasca, and DMT, activating mania in some individuals (e.g., Lake et al., 1981; Szmulewicz et al., 2015; Umut et al., 2011). Thus, while the evidence is not clear that manic symptoms are activated by these compounds, caution is warranted, especially in individuals with a history or risk of mania.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

2.3.1.1 GENERAL APPROACH TO RISK AND MITIGATION IN THIS STUDY

The clinical safety of psilocybin has been studied extensively in open-label and double-blind controlled trials, using oral dosages ranging from 0.98 mg/70 kg to 42 mg/ 70 kg. Psilocybin is generally well-tolerated (Brown et al., 2017; J. van Amsterdam et al., 2011), and contemporary clinical trials that employ rigorous screening and supervised administration of psilocybin have reported no serious adverse events (Bogenschutz & Ross, 2016; Dos Santos et al., 2020). In addition, a meta-analysis of eight double blind, placebo-controlled experiments in which psilocybin was administered to healthy people found that all adverse drug reactions were successfully managed through interpersonal support and did not require psychopharmacological intervention (Studerus et al., 2011).

However, a conservative assessment of potential risks to participants in this study is critical given that no prior studies have administered psilocybin to patients with a known diagnosis of BD 2 or any bipolar disorder. This study includes structural features designed to minimize risk across multiple categories:

- Psilocybin dose-escalation protocol:
    - We will use a low-moderate initial dose of psilocybin (10mg) followed by a potential second dose, a moderate-high dose (25mg) if the first dose is well-tolerated according to clinician assessments and participant reports and the participant's depression has not remitted at 21 days post administration of the initial dose. The initial dose will be significantly lower than those used in prior contemporary clinical trials (Griffiths et al., 2006; Ross et al., 2016). This conservative, optional dose-escalation protocol will help participants accommodate to the effects of psilocybin and allow assessment of each participant's response to a lower dosage of psilocybin prior to administration of the higher, more typical therapeutic dosage. Additionally, it is possible that the lower 10 mg dosage will be therapeutic for some individuals in this population. Thus, if a participant's depression remits (indicating a therapeutic response) 21 days after the initial 10 mg dosage, that participant will not be given the second dosage and will instead be followed for the remainder of the study period. This will avoid exposing participants unnecessarily to higher doses of psilocybin.
- Study staff expertise:
    - A study physician with prior experience conducting clinical psilocybin research will oversee procedures and assessments in this trial. At least one licensed mental health professional, will be present with participants throughout each drug administration day and will provide oversight for all preparation and integration sessions being completed by staff currently in training to obtain licensure. All study staff who will interact with participants will have training on best practices for psychedelic research, emergency protocols, and the particular needs of research participants in psychedelic trials.
- Extended observation post-psilocybin administration sessions:
    - Participants will be given the contact information for the on-call study team who will be available for after the psilocybin dosing session for any concerns. They will be instructed to contact emergency services for and medical or psychiatric emergencies, and let the study team know after.
    - To monitor for hypomania (or mania) signs, we will ask participants about their sleep 7 days after their psilocybin dosing session.

- Location at UCSF Medical Center:

    - The research unit is located at UCSF Mission Bay in the UCSF Nancy Friend Pritzker Psychiatry Building at Mission Bay, one block away from the main hospital campus. Research staff will provide participants specific instructions on the location of each visit upon scheduling. Participants on either research unit have access to emergency services, inpatient medical services, and psychiatric services. Participants can be transferred promptly to the hospital in the event that a higher level of care becomes necessary.

2.3.1.2 IMMEDIATE RISKS ASSOCIATED WITH PSILOCYBIN AND MITIGATION STRATEGIES

The IB for psilocybin summarizes adverse event data from previous clinical trials. We have used these data to categorize and evaluate potential risks, giving particular consideration to risks that may be elevated among people with BD 2; these are as follows:

- Physiological toxicity:

    - Symptoms such as dizziness, weakness, tremors, nausea, vomiting, drowsiness, paresthesia, blurred vision, dilated pupils, and increased tendon reflexes have been reported after ingestion of psilocybin or similar hallucinogens (Hollister, 1961; D. E. Nichols, 2004). The most common adverse effect reported is a transient headache (Garcia-Romeu et al., 2016; Johnson et al., 2012), which may be the result of 5-HT receptor-mediated vascular constriction and relaxation (D. E. Nichols, 2016). Psilocybin ingestion may also cause dose-dependent mild to moderate increases in heart rate, systolic and diastolic blood pressure, as well as mild increases in hormone levels such as thyroid-stimulating hormone (TSH), prolactin, and cortisol. These changes are thought to stem primarily from acute hypothalamic-pituitary-adrenal (HPA) axis activation and are transient in healthy humans (Hasler et al., 2004; Passie et al., 2002). There is no evidence of an effect of psilocybin on EKG from a study (Hasler et al., 2004) that examined acute physiological changes induced by a range of doses (0.045 mg/kg-0.315mg/kg; approximately 3-22 mg).

    - We will minimize these risks by:

        - Screening potential participants and excluding those with significant cardiovascular autonomic dysfunction or other medical conditions that may increase the likelihood of physiological toxicity (e.g., inadequately controlled hypertension, insulin-dependent diabetes).

        - Conducting full physical exams and laboratory testing during screening to detect baseline abnormalities that may increase risk of physiological toxicity.

        - Measuring blood pressure prior to each psilocybin administration. Study staff will respond to readings outside of the pre-specified safety parameters as described in Section 8: Study Assessments and Procedures

        - Measuring heart rate prior to each psilocybin administration. Study staff will respond to readings outside of the pre-specified safety parameters as described in Section 8: Study Assessments and Procedures

- Measuring heart rate and blood pressure readings periodically during the period of acute psilocybin effects. Study staff will respond to readings outside of the pre-specified safety parameters as described in Section 8: Study Assessments and Procedures

- Supervising participants closely when they stand or ambulate and providing assistance if necessary to prevent falls during the period of acute psilocybin effects. At least one facilitator will accompany a participant to the restroom located outside the psilocybin administration room.

- After each psilocybin administration and after participants are cleared to leave the research unit by the on-site physician

– <u>Acute psychological distress:</u>

- Psilocybin ingestion may lead to distress characterized by logorrhea, anxiety, disorientation, dissociation, fear/panic, dysphoria, visual hallucinations, or paranoia (Griffiths et al., 2006, 2011). In unprepared individuals or in unsupervised situations, this distress could potentially escalate to dangerous behavior. In previous contemporary clinical trials, participants' distress has responded well to reassurance/interpersonal support, has not required pharmacological intervention, and has resolved by the end of the psilocybin administration day (Carhart-Harris et al., 2016; Johnson et al., 2008). Importantly, even in cases where participants reported elevated anxiety or fear, the majority of psilocybin administration sessions were still described by participants as personally meaningful and did not result in decreased well-being or life satisfaction (Griffiths et al., 2006, 2011).

- We will minimize these risks by:

  - Conducting multiple preparatory sessions prior to psilocybin administration according to best practices (Johnson et al., 2008) during which trained facilitator(s) will build rapport with participants, discuss the possibility of experiencing distress during the period of acute psilocybin effects, and answer participants' questions regarding potential psilocybin effects. Participants will engage in simulated drug administration sessions with the facilitator(s) during these preparatory sessions to increase their comfort with the study procedures and the physical environment in which psilocybin will be administered.

  - Conducting psilocybin administration sessions in a calming, pleasant room within the research unit at UCSF. This environment has been designed with consideration of the perceptual changes and disorientation that participants may experience during psilocybin sessions. Potentially dangerous furniture or other objects are avoided, windows cannot be opened wide enough to pose a safety risk, and no telephones, pagers, or other devices that may cause distressing sounds are permitted during the sessions.

  - Securing participants' keys, mobile devices, shoes, and other personal belongings prior to psilocybin administration to discourage leaving the research unit during the period of acute psilocybin effects.

- Having at least one trained facilitator present throughout the psilocybin administration sessions to offer psychological support, help the participant manage any distress that may arise, and use verbal de-escalation techniques to ensure the participant remains physically safe on the research unit.

- Preparing facilitators and participants for the possibility of a non-routine event (e.g., a fire alarm) during psilocybin administration sessions. Facilitators will be instructed to remain in close contact with a participant during a non-routine event whenever possible.

- On psilocybin administration days, having rescue medications available if reassurance/interpersonal support fails to reduce acute psychological distress. Per safety recommendations for clinical trials involving psychedelics (Johnson et al., 2008), benzodiazepine anxiolytics and/or antipsychotic medications can be administered by a study clinician if necessary.

- Conducting multiple integration sessions following psilocybin administration according to best practices (Johnson et al., 2008) during which at least one trained facilitator will meet with each participant to ensure psychological stability and provide the opportunity for participants to discuss their experience during the psilocybin administration sessions and process the impact of these sessions.

– Drug interactions:

- Tryptamine psychedelics like psilocybin modulate multiple targets and may interact with agents within several drug classes in a complex manner (D. E. Nichols, 2016; Ray, 2010). For instance, chronic administration of tricyclic antidepressants and lithium (Bonson & Murphy, 1996) and acute administration of serotonin reuptake inhibitors (Fiorella et al., 1996) and the antipsychotic haloperidol (Geyer & Vollenweider, 2008) have been shown to potentiate psychedelic effects. In contrast, chronic administration of serotonin reuptake inhibitors (Bonson & Murphy, 1996; Stolz et al., 1983; Strassman, 1992) and monoamine oxidase inhibitors (MAOIs; Bonson & Murphy, 1996) have been shown to attenuate the response to serotonergic psychedelics like psilocybin (Bonson 1996).

- People with BD 2 may take multiple medications that modulate serotonergic activity, such as antidepressants, that increase the risk of a potentially fatal serotonin syndrome (Bartlett, 2017). Serotonin syndrome is caused by excess serotonergic agonism in both the central (CNS) and peripheral nervous systems (PNS) and often manifests as a clinical triad of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities with rapid onset (Boyer & Shannon, 2005). It is thought to be rare, but the incidence is unknown, as is the number of cases that are mild, moderate or severe (Scotton et al., 2019). Several drugs and drug interactions have been associated with serotonin syndrome; management involves discontinuing the precipitating drugs, supportive care, benzodiazepine administration to reduce agitation, and controlling autonomic instability and hyperthermia in more severe cases (Boyer & Shannon, 2005). Importantly, serotonin syndrome is not an idiopathic drug reaction but a predictable consequence of increasing levels of free serotonin or 5-HT receptor activation.

- We will minimize these risks by:

- Screening potential participants and excluding those taking medications or supplements that may have significant interactions with psilocybin (See Section 5.2 Exclusion Criteria).

- Monitoring participants for signs of serotonin syndrome during the period of acute psilocybin effects. If a participant shows any concerning signs (increased tremor, spontaneous clonus, muscle rigidity, temperature >38 degrees Celsius, agitation, or diaphoresis), the on-site study clinician will conduct an immediate evaluation and make an appropriate treatment plan that may include administration of benzodiazepines and/or escalation of care if necessary.

2.3.1.3 LONG-RANGE RISKS ASSOCIATED WITH PSILOCYBIN AND MITIGATION STRATEGIES.

– Prolonged psychosis and mania:

- In contrast to acute psychological distress, cases of prolonged psychosis are extremely rare in well-screened and prepared participants. A meta-analysis of eight double blind, placebo-controlled experiments (dose range 0.115-0.315 mg/kg) in 110 healthy people found no evidence of prolonged psychosis following psilocybin administration in any participants (Studerus et al., 2011). However, while hallucinogens such as psilocybin are not thought to precipitate new psychotic disorders, they may unmask a psychotic disorder in those who are susceptible (Geyer & Vollenweider, 2008). In one study of recreational psilocybin use in over 1990 participants, three individuals reported what appeared to be sustained enduring and impairing psychotic symptoms, although all three individuals were young men between the ages of 18-21 years old (outside of the age range of the present study) (Carbonaro et al., 2016).

- As mentioned above, there are no reported cases in modern clinical trials of the activation of mania, beyond the initial common euphoric effects of the drug onset and the 'afterglow' of the effects approximately 24 hours after (e.g., Rucker et al., 2018; Studerus et al., 2011), although it should be noted that all studies thus far have excluded participants with bipolar disorder or, in many cases, a family history of bipolar disorder. That said, to our knowledge there are no case report examples of prolonged mania after psilocybin use. However, there are a number of case reports of recreational and community guided use of LSD, ayahuasca, and DMT activating mania in some individuals (e.g., Lake et al., 1981; Szmulewicz et al., 2015; Umut et al., 2011). For example, Szmulewicz et al. (2015) reported on a case of a 30-year-old man who experienced a manic episode two days after participating in a 4-day ayahuasca ritual in Brazil. A thorough review of his history indicated a likely hypomanic episode two weeks prior to travel to Brazil. The manic episode he experienced two days after the 4-day ayahuasca rituals was severe enough to require hospitalization, but he was asymptomatic on medication one month post discharge. The authors conclude that the "antidepressant-induced mania [was] due to excessively prolonged use of a substance with antidepressant properties", i.e., the 4 day ayahuasca ritual (Szmulewicz et al., 2015, pg. 2). In another case example, a 19 year old male who reported chronic use of cannabis, had what appears to have been a manic episode with psychosis after using a combination of cannabis and DMT twice in a two-week period (Umut et al., 2011), which led him to ultimately be hospitalized for 12 days. He was later treated successfully with antipsychotics and his symptoms remitted. In a review of adverse events of the União do Vegetal ayahuasca rituals in Brazil

between 1994-2007 (with more than 25,000 individual uses of the substance), Lima et al. (2011) found approximately 51 psychiatric adverse events either during or shortly after the administration of the substance, of which 4 were described as a manic or psychotic/manic episode. While this number is lower than the base rate of mania or psychosis in the general population (and individuals are not typically screened for psychosis or mania for these rituals), it is possible that these episodes were activated by the hallucinogenic substance, and that these individuals would not have had these manic or psychotic experiences without it.

- In summary, while there is a relative lack of evidence of mania activation by psilocybin in the literature, individuals with bipolar disorders have been excluded from modern trials, and further there are cases of mania activation using other hallucinogenic compounds in community and religious ritual settings. Furthermore, given the possible risk of activating mania by serotonergic agents in this population (e.g., Amsterdam & Shults, 2010; Goodwin & Ghaemi, 2003), it is reasonable to assume that people with BD 2 may be at elevated risk of developing manic symptoms with psilocybin ingestion.

- We will minimize these risks of activating enduring psychosis or mania by:

    - Screening potential participants and excluding those with any history of a psychotic disorder or psychotic symptoms, or any history of mania.

    - Using a number of specific measures of mania and psychosis and multiple sources (researcher assessments, therapist assessments, participant reports, and caregiver/important other reports) to quantify the full potential range of manic and psychotic symptoms observed in bipolar disorders in order to ensure early detection and prompt treatment of any manic or psychotic symptoms that may develop.

    - Assessing manic and psychotic symptoms on the morning of each psilocybin administration session (prior to dosing), on the morning following each psilocybin administration session, and at multiple timepoints following psilocybin administration. On days when there is no formal assessment during the two weeks after dosing, the facilitator(s) will have brief phone check-ins with the participant to ensure that they are not at heightened risk. These procedures will ensure prompt detection, evaluation by study clinicians, and appropriate treatment in coordination with a participant's outside mental health provider if necessary. See Section 1.3 Schedule of Activities for all assessment timepoints.

    - Using a smaller initial dose (10 mg) than has been used in previous trials to test for safety and tolerability. We will only use the higher 25 mg dose if the first dose is well tolerated and the participant's depression is not remitted 3 weeks after the initial dose. This will maximize safety and minimize exposing participant's to unnecessary risk.

    - Communicating with a support-person who has contact with the participant at least five days a week and will be able to monitor changes in behavior.

    - In addition to the scheduled integration and assessment visits, we will call the participant each day after the dosing sessions for two weeks to check in with the

participant on how they are doing. These informal assessments will augment the longer assessment and integration meetings.

- Lasting perceptual abnormalities:

  - Persistent, distressing alterations in perception lasting from weeks to years after serotonergic hallucination use have been reported (Espiard et al., 2005) and diagnosed as hallucinogen persistent perception disorder (HPPD). The incidence of HPPD is unknown, but it is thought to be rare given the few reported cases out of millions of hallucinogen doses administered since the 1960s (Halpern & Pope, 2003; Litjens et al., 2014). The meta-analysis by Studerus et al. (2011) found no significant increase in perceptual disturbances following the experimental drug sessions and no evidence of HPPD in any participants. In contemporary clinical trials that involve rigorous screening and preparation, there have been no reported cases of HPPD.

  - We will minimize these risks by screening potential participants and excluding those with any history of HPPD or other significant perceptual disturbances following hallucinogen use. Steps taken to minimize the risk of prolonged psychosis (detailed above) will also help to minimize the risk of lasting perceptual abnormalities.

- Abuse and dependence:

  - Like other psychoactive drugs, psilocybin may be used in a manner that threatens safety or well-being. However, psilocybin is not considered to be a drug of dependence in that it has not been shown to precipitate compulsive drug seeking behavior in humans (Johnson et al., 2018; O'Brien, 2011) or in animals (Fantegrossi et al., 2004; Poling, 1979; Sakloth et al., 2019). Furthermore, hallucinogens like psilocybin have not been associated with a withdrawal syndrome (O'Brien, 2011). In the meta-analysis by Studerus et al. (2011), the vast majority of participants (approximately 90%) reported "no change" in their psilocybin use following their psilocybin administration sessions, as well as "no change" in overall drug use. Those who did report changes often described decreased consumption (see Table 5 in Studerus et al., 2011). More participants reported using psilocybin less often after their laboratory sessions (5.6% of all participants) than more often (3.3% of all participants). In addition, epidemiological data from 44,000 illicit opioid users who completed the National Survey on Drug Use and Health from 2008 to 2013 indicate that psychedelic drug use is associated with a reduced risk of opioid abuse and opioid dependence (Pisano et al., 2017). Given these findings, administration of psilocybin in this study is unlikely to lead to physical or psychological dependence.

  - We will minimize these risks by:

    - Screening potential participants and excluding those with a substance use disorder in the past year.

    - Administering psilocybin only under clinical supervision in a restricted setting; participants will not have access to the drug outside of this setting in the research unit at UCSF.

    - Complying with all local and national requirements pertaining to clinical research with controlled substances and the PI will maintain current registration with authorities with

oversight of controlled substances. These precautions, along with the Drug Accountability process, documentation, and monitoring, will reduce the chance of drug diversion. See Section 6.2 Drug Storage, Handling, and Accountability.

2.3.1.4 OTHER RISKS RELATED TO PARTICIPATION IN THIS STUDY AND MITIGATION STRATEGIES

- Risk of worsening depression:

  - Participants could experience an exacerbation of depressive symptoms during participation in this study. However, all participants will be in ongoing therapy sessions with their assigned facilitator throughout the duration of the trial. Though there have been recent reports of increased suicidal ideation or behavior in modern trials of psilocybin ((Goodwin, Guy M., et al. "Single-dose psilocybin for a treatment-resistant episode of major depression." New England Journal of Medicine 387.18 (2022): 1637-1648.). In other cases, psilocybin may in fact have anti-suicide effects (Hendricks et al., 2015).

  - We will minimize this risk by:

    - Assessing depressive symptoms at Baseline, on the morning of each psilocybin administration session (prior to dosing), and at multiple timepoints following psilocybin administration to ensure prompt detection of any worsening symptoms, evaluation by study clinicians, and appropriate treatment in coordination with a participant's outside mental health clinician if necessary. See Section 1.3 Schedule of Activities for all assessment timepoints.

    - If additional treatment or escalation of care is warranted at any time, study clinicians will attempt to notify outside mental health clinicians and help to develop an appropriate treatment plan.

    - The facilitator(s) will have frequent contact with the participants for the two weeks after dosing. This will allow prompt detection, evaluation, and treatment of any worsening of psychiatric symptoms.

- Risk associated with collection of sensitive information:

  - Collecting sensitive information at various time points introduces the risk of such information being disclosed due to errors or data breaches. Both the PI and participants may be at risk for a violation of privacy and/or loss of confidentiality. This risk will increase as the study progresses as ongoing health information will be collected.

  - We will minimize this risk by:

    - Adhering to best practices for the collection, storage, and use of potentially sensitive information at all stages of the study. All identifiable data will be stored on a secure electronic database coded by a participant identification number. These data will be stored separately from any materials that would identify participants.

- Having all research staff maintain up-to-date human subjects training per institutional requirements to ensure the proper conduct of scientific research in humans.

- Obtaining a Certificate of Confidentiality (CoC) (See Section 10.1.3).

– Risk associated with blood draws:

- Venipuncture can be associated with discomfort, bruising, infection, bleeding and fainting. The amount of blood drawn as part of screening for this study will not have adverse physiological effects. The risk of accidental needle sticks during sample collection resulting in infection from blood borne pathogens is extremely low.

- We will minimize these risks by ensuring that certified phlebotomists use standard sterile procedures for drawing blood per institutional requirements and asking all participants about a history of fainting prior to venipuncture (participants with a positive history will be reclined during the procedure).

2.3.2 KNOWN POTENTIAL BENEFITS

2.3.2.1 IMMEDIATE POTENTIAL BENEFITS

Based on data from prior studies, participants may experience intense happiness, pleasant unusual sensory experiences, and/or a profound sense of peace/harmony during the period of acute psilocybin effects (Griffiths et al., 2006). Participants may also experience rapid, significant improvements in depression and/or quality of life, as has been observed in multiple clinical studies (Anderson et al., 2020; Carhart-Harris, Bolstridge, et al., 2018; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016).

2.3.2.2 LONG-RANGE POTENTIAL BENEFITS

Given evidence that the beneficial effects of psilocybin may extend for months following use (Griffiths et al., 2006; Studerus et al., 2011), participants may experience positive changes in depression and anxiety as well as their outlook, sense of well-being, and life satisfaction. These changes may, in turn, improve participants' level of function and reduce caregiver/important other burden. In addition, participants may find the experience of completing psilocybin treatment highly meaningful, as reported by other investigators (Griffiths et al., 2006). Participants will also have the knowledge that they are contributing to scientific investigation that may benefit other people with BD 2 in the future, which may provide personal satisfaction. Finally, findings from this study will provide critical data on the potential clinical utility of psilocybin treatment for people with BD 2 and clinically significant depression or anxiety, offering benefits at a societal level.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

2.3.3.1 RATIONALE FOR EXPOSING PARTICIPANTS TO POTENTIAL RISKS

Depression is a common and disabling symptom among people with BD 2 for which currently available treatments are inadequate (Gitlin, 2018; Ruggero et al., 2007). Psilocybin treatment has demonstrated significant promise in other medically complex populations with similar symptoms including people with life-threatening cancer (Griffiths

et al., 2016; Grob et al., 2011; Ross et al., 2016) and long-term AIDS survivors (Anderson et al., 2020). Because previous trials have excluded potential participants with bipolar disorder, we currently lack the safety and feasibility data needed to examine psilocybin's clinical utility for depression in BD 2. Our study will lay critical groundwork for future investigations.

Furthermore, in previous trials, persistent beneficial effects of psilocybin have been observed after only one or two dosing sessions. These findings suggest that it may be possible to significantly improve depression without chronic exposure to an additional pharmacologic agent. Reducing polypharmacy among patients with BD 2, is a major potential benefit of psilocybin treatment.

2.3.3.2 SUMMARY OF RISK-MITIGATING STRATEGIES

We have included extensive risk mitigation strategies in this trial, including:

- Careful screening and exclusions
- Administration of psilocybin in a controlled research unit
- Use of a low-moderate initial psilocybin dose followed by optional dose escalation to test drug tolerance
- Extensive monitoring during and after psilocybin administration sessions by clinicians and facilitator(s) with expertise in psychedelic treatment
- All participants will be engaged in active mental health treatment throughout the trial
- Use of established best practices for maximizing safety in clinical trials involving psychedelic administration, including appropriate preparation and integration sessions
- Follow-up to three months after the last psilocybin administration

2.3.3.3 RISK VERSUS BENEFIT ASSESSMENT

Though there are clear theoretical risks to administering psilocybin to people with BD 2, psilocybin treatment has the potential to significantly improve outcomes for patients living with this disorder. Both epidemiological studies and modern clinical trials administering psilocybin in controlled settings demonstrate a largely benign safety profile for the drug (Carhart-Harris & Nutt, 2013; J. van Amsterdam et al., 2011), but no previous trials have included patients with BD 2 or any bipolar disorder. Evaluating the safety and feasibility of this treatment approach is an essential next step. Given the reassuring safety data gathered in previous psilocybin trials and the extensive risk mitigation strategies employed in this study, the potential benefits of examining the safety and feasibility of psilocybin treatment for depression in BD 2 outweigh the risks.

3 OBJECTIVES AND ENDPOINTS

3.1 PRIMARY OBJECTIVE

The primary objective of this study is to examine the safety, tolerability, and feasibility of psilocybin treatment for depression in people with BD 2.

3.2 PRIMARY ENDPOINTS

3.2.1 SAFETY AND TOLERABILITY ENDPOINTS

Safety and tolerability will be evaluated continually using multiple monitoring and assessment procedures (see below and Section 1.3 Schedule of Activities) during and following the first psilocybin session (Day A0) and, if depression has not remitted, the second psilocybin session (Day B0). A Safety Monitoring Committee (SMC; see Section 10.1.6) will review all safety and tolerability data. In addition to Adverse Event (AE) monitoring, we will monitor for any changes specifically in participants' BD 2 symptoms and development of any psychotic symptoms. Measures and specific endpoints are as follows:

- Adverse Events (AEs) including Treatment-Emergent AEs (TEAEs) and Serious AEs (SAEs). AEs will be measured by vital sign monitoring, physical exams, clinician-administered assessments, participant reports, caregiver/important other reports, guide reports, and phone check-ins.
    - Incidence of AEs by severity
    - Incidence of AEs requiring medical/psychiatric attention
    - Incidence of AEs leading to withdrawal/termination from the study
    - Incidence of new concomitant medications
    - Incidence of TEAEs
    - Incidence of TEAEs by severity
    - Incidence of solicited AEs
    - Incidence of solicited AEs by severity
    - Incidence of SAEs
    - Incidence of new concomitant medications
    - Incidence of clinically significant abnormalities on physical examination

- Clinical Global Impression - Improvement scale (CGI-I). Any indication from the following measures (of mania, depression, suicidality, or psychosis) that leads the study staff to suspect that the patient's condition is worsening warrants a score of 6 or greater on the CGI-I. At this point the study staff will determine the best clinical course of action (e.g., involvement of the participants mental health professional, removal from any further dose (if one remains), or hospitalization).

    - At any point in the study if the CGI-I score is rated a 6 "much worse."
    - CGI-I will be assessed at every in-person clinician visit assessment or integration meeting.

- Manic and psychotic symptoms (participant-reported)

- Measure: Altman Self-Rating Mania Scale (ASRM-14). The ASRM is a 14-item questionnaire with each item rated on a 0 to 4 scale. The scale ranges from 0-56 with higher scores indicating greater severity of manic symptoms, with items that also measure psychosis.

- Endpoints
    - Change in ASRM-14 from Initial Phone Screen to Day A0 (immediately prior to dosing)
    - Change in ASRM-14 from Initial Phone Screen to Day A4
    - Change in ASRM-14 from Initial Phone Screen to Day A11

  If the second dose of psilocybin is required:
    - Change in ASRM-14 from Initial Phone Screen to Day B0 (immediately prior to dosing)
    - Change in ASRM-14 from Initial Phone Screen to Day B4
    - Change in ASRM-14 from Initial Phone Screen to Day B11

– Manic symptoms (clinician-assessed)

- Measure: Young Mania Scale (YMS). The YMS is an 11-item questionnaire. 7 items are rated on a 0 to 4 scale, while the remaining 4 items are rated on a 0-8 scale. The total scale ranges from 0-60 with higher scores indicating greater severity of manic symptoms. A total score ≤12=remission, 13-19=minimal symptoms, 20-25=mild mania, 26-37=moderate mania, and 38-60=severe mania

- Endpoints
    - Change in YMS from Screening/Baseline Assessment to Prep Visit 2
    - Change in YMS from Screening/Baseline Assessment to Day A1
    - Change in YMS from Screening/Baseline Assessment to Day A7
    - Change in YMS from Screening/Baseline Assessment to Day A14
    - Change in YMS from Screening/Baseline Assessment to Day A21

  If the participant remits at Day A21:
    - Change in YMS from Screening/Baseline Assessment to Day A90
    - Change in YMS from Screening/Baseline Assessment to Day A365

  If the second dose of psilocybin is required (participant's depression does not remit):
    - Change in YMS from Screening/Baseline Assessment to Day B1
    - Change in YMS from Screening/Baseline Assessment to Day B7
    - Change in YMS from Screening/Baseline Assessment to Day B14
    - Change in YMS from Screening/Baseline Assessment to Day B21
    - Change in YMS from Screening/Baseline Assessment to Day B90
    - Change in YMS from Screening/Baseline Assessment to Day B365

– Suicidality symptoms (clinician-assessed)

- Measure: Columbia-Suicide Severity Rating Scale (C-SSRS). The C-SSRS characterizes suicidal ideation (5 items with binary (yes/no) responses), intensity of ideation (5 items rated on a 0-5 scale), and suicidal behavior (6 items with binary (yes/no) responses) in three separate categories. Any score greater than 0 for suicidal ideation may indicate need for medical intervention. Intensity of ideation has a total score range of 0-25 with higher scores indicating greater severity. Suicidal behavior is rated by it's first item actual lethality with 0=no physical damage, 1=minor physical damage, 2=moderate physical damage, 3=moderately severe damage,

4=severe physical damage. If actual lethality is 0, suicidal behavior is further categorized by remaining items with 0=behavior not likely to result in injury, 1=behavior likely to result in injury but not likely to cause death, 2=behavior likely to result in death despite available medical care.

- Endpoints:
    - Change in C-SSRS from Screening/Baseline Assessment to Prep Visit 2
    - Change in C-SSRS from Screening/Baseline Assessment to Day A1
    - Change in C-SSRS from Screening/Baseline Assessment to Day A7
    - Change in C-SSRS from Screening/Baseline Assessment Day A14
    - Change in C-SSRS from Screening/Baseline Assessment Day A21

    If the participant remits at Day A21:
    - Change in C-SSRS from Screening/Baseline Assessment to Day A90
    - Change in C-SSRS from Screening/Baseline Assessment to Day A365

    If a second dose of psilocybin is required:
    - Change in C-SSRS from Screening/Baseline Assessment to Day B1
    - Change in C-SSRS from Screening/Baseline Assessment to Day B7
    - Change in C-SSRS from Screening/Baseline Assessment to Day B14
    - Change in C-SSRS from Screening/Baseline Assessment to Day B21
    - Change in C-SSRS from Screening/Baseline Assessment to Day B90
    - Change in C-SSRS from Screening/Baseline Assessment to Day B365

– Positive psychotic symptoms (clinician-assessed)

- Measure: Positive and Negative Syndrome Scale (PANSS). The PANSS is a 30-item questionnaire rated on a 7-point scale (1=”absent” to 7=”extreme”). It includes 7 positive symptom items. The positive scale ranges from 7-49 with higher scores indicate greater severity of symptoms.

- Endpoints
    - Change in positive symptoms in PANSS from Screening/Baseline Assessment to Prep Visit 2
    - Change in positive symptoms in PANSS from Screening/Baseline Assessment to Day A1
    - Change in positive symptoms in PANSS from Screening/Baseline Assessment to Day A7
    - Change in positive symptoms in PANSS from Screening/Baseline Assessment to Day A14
    - Change in positive symptoms in PANSS from Screening/Baseline Assessment to Day A21

    If the participant remits at Day A21:
    - Change in positive symptoms in PANSS from Screening/Baseline Assessment to Day A90
    - Change in positive symptoms in PANSS from Screening/Baseline Assessment to Day A365

    If a second dose of psilocybin is required:
    - Change in positive symptoms in PANSS from Screening/Baseline Assessment to Day B1
    - Change in positive symptoms in PANSS from Screening/Baseline Assessment to Day B7
    - Change in positive symptoms in PANSS from Screening/Baseline Assessment to Day B14
    - Change in positive symptoms in PANSS from Screening/Baseline Assessment to Day B21
    - Change in positive symptoms in PANSS from Screening/Baseline Assessment to Day B90
    - Change in positive symptoms in PANSS from Screening/Baseline Assessment to Day A635

- Support person-reported outcomes

  - Measure: Mood Disorder Burden Interview (MDBI). The MDBI is a 64-item questionnaire that assesses burden with 32 experiences. For each experience, the support person is asked to report the frequency of that experience and then asked to report how upset they were by that experience. The Frequency items are rated on a 4-point scale (0 “never” to 3 “nearly always”), and the Reaction items are rated on a 5-point scale (0 “not at all” to 4 “extremely”).

  - Endpoints
    - Change in support person-reported symptoms from Screening/Baseline Assessment to Day A7
    - Change in support person-reported symptoms from Screening/Baseline Assessment to Day A21

    If the participant remits at Day A21:
    - Change in support person-reported symptoms from Screening/Baseline Assessment to Day A90

    If the second dose of psilocybin is required:
    - Change in support person-reported symptoms from Screening/Baseline Assessment to Day B7
    - Change in support person-reported symptoms from Screening/Baseline Assessment to Day B21
    - Change in support person-reported symptoms from Screening/Baseline Assessment to Day B90

- Therapist-reported symptoms

  - Measure: modified PHQ-9 and ASRM-14. The PHQ-9 is a 9-item measure that assesses the severity of depressive symptoms in individuals. Each item on the measure is rated on a 4-point scale (0=Not at all; 1=Several days; 2=More than half the days; and 3=Nearly every day). The total score can range from 0 to 27, with higher scores indicating greater severity of depression. The ASRM-14 is a 14-item questionnaire with each item rated on a 0-4 scale. The scale ranges from 0-56 with higher scores indicating greater severity of manic symptoms. Both measures will be modified for the therapist to report on the symptoms observed in the patient.

  - Endpoints:
    - Change in therapist-reported symptoms from Screening/Baseline Assessment to Day A21

    If the participant remits at Day A21:
    - Change in therapist-reported symptoms from Screening/Baseline Assessment to Day A90

    If a second dose of psilocybin is required:
    - Change in therapist-reported symptoms from Screening/Baseline Assessment to Day B21
    - Change in therapist-reported symptoms from Screening/Baseline Assessment to Day B90

3.2.2 FEASIBILITY ENDPOINTS

Feasibility will be evaluated using standard measures as well as study-specific questionnaires. Specific endpoints:

1. Participant recruitment rate: Feasibility of recruitment will be assessed as a percentage of participants who were contacted for pre-screening and consented.
2. Participant retention rate: Retention feasibility will be assessed as a percentage of participants who began and completed treatment.
3. Participant-reported acceptability of study procedures
    - Measure: Study-specific Treatment Satisfaction Questionnaire - Participant (TSQ-P)
    - Endpoints
        If the participant remits at Day A21:
        - Change in TSQ-P from Screening/Baseline Assessment to Day A90

        If a second dose of psilocybin is required:
        - Change in TSQ-P from Screening/Baseline Assessment to Day B90
        - Support person-reported acceptability of study procedures
    - Measure: Study-specific Treatment Satisfaction Questionnaire - Support Person (TSQ-S)
    - Endpoints:
        If the participant remits at Day A21:
        - Change in TSQ-S from Screening/Baseline Assessment to Day A90

        If a second dose of psilocybin is required:
        - Change in TSQ-S from Screening/Baseline Assessment to Day B90

3.3 Exploratory Objective

The exploratory objective of this study is to examine the potential efficacy of psilocybin treatment for improving clinically significant depression in people with BD 2.

3.4 Exploratory Endpoints

3.4.1 Primary Efficacy Endpoint

The potential impact of psilocybin treatment on depressive symptoms will be evaluated primarily using clinician-administered assessments. The Primary Endpoint will be three weeks following the final psilocybin administration session (Day A21 or Day B21). Specific endpoint:

1. Depressive symptoms (clinician-assessed)

    - Measure: Montgomery-Asberg Depression Rating Scale (MADRS). The MADRS is a 10-item questionnaire, with each item assigned a score ranging from 0 ("normal/not present") to 6 ("extreme"). Scoring is based on the ten items with total scores ranging from 0 to 60. Recommended severity ratings for bipolar depression are: 0–6 for no depression, 7–19 for mild depression, 20–34 for moderate depression, and ≥35 for severe depression.

    - Endpoint
        If the participant remits (i.e., a MADRS score of 6 or less) at Day A21:
        - Change in MADRS from Screening/Baseline Assessment to Day A21

        If second dose of psilocybin is required:

- Change in MADRS from Screening/Baseline Assessment to Day B21

3.4.2 SECONDARY EFFICACY ENDPOINTS:

To further characterize the potential impact of psilocybin treatment, depressive symptoms, and multiple aspects of function will be assessed using participant, support person, therapist, and clinician-reported measures. Measures and specific endpoints:

1. Depressive symptoms (clinician-assessed)

   - Measure: Montgomery-Asberg Depression Rating Scale (MADRS). The MADRS is a 10-item questionnaire, with each item assigned a score ranging from 0 ("normal/not present") to 6 ("extreme"). Scoring is based on the ten items with total scores ranging from 0 to 60. Recommended severity ratings for bipolar depression are: 0–6 for no depression, 7–19 for mild depression, 20–34 for moderate depression, and ≥35 for severe depression.

   - Endpoint
     - Change in MADRS from Screening/Baseline Assessment to Prep 2
     - Change in MADRS from Screening/Baseline Assessment to Day A7
     - Change in MADRS from Screening/Baseline Assessment to Day A14

     If the participant remits at Day A21:
     - Change in MADRS from Screening/Baseline Assessment to Day A90
     - Change in MADRS from Screening/Baseline Assessment to Day A365

     If a second dose of psilocybin is required:
     - Change in MADRS from Screening/Baseline Assessment to Day B7
     - Change in MADRS from Screening/Baseline Assessment to Day B14
     - Change in MADRS from Screening/Baseline Assessment to Day B90
     - Change in MADRS from Screening/Baseline Assessment to Day B365

2. Depressive symptoms and anxiety symptoms (participant-reported)

   - Quick Inventory of Depressive Symptomatology (QIDS-SR). The QIDS-SR is a 16-item questionnaire used to rate the 9 symptoms of a major depressive episode. Each item is rated on a scale from 0-3. For symptoms that are evaluated by multiple items, the highest scoring item is taken. The total score ranges from 0-27. Scores of 0-5=none, 6-10=mild, 11-15=moderate, 16-20=severe, 21-27=very severe.

   - Endpoints
     - Change in QIDS-SR from Prep Visit 2 to Day A0 (immediately prior to psilocybin dosing)
     - Change in QIDS-SR from Prep Visit 2 to phone call Day A4
     - Change in QIDS-SR from Prep Visit 2 to phone call Day A11
     - Change in QIDS-SR from Prep Visit 2 to phone call Day A90

     If a second dose of psilocybin is required:
     - Change in QIDS-SR from Prep Visit 2 to Day B0 (immediately prior to psilocybin dosing)
     - Change in QIDS-SR from Prep Visit 2 to phone call Day B4
     - Change in QIDS-SR from Prep Visit 2 to phone call Day B11
     - Change in QIDS-SR from Prep Visit 2 to phone call Day B90

3. Sleep quality (participant-reported)

    - Measure: Insomnia Severity Index (ISI). The ISI is a 7-item questionnaire rated on a 5-point scale (0 to 4). The total raw score ranges from 0-28 with higher score indicating greater severity in sleep disturbance. Score of 0-7=no clinically significant insomnia, 8-14=subthreshold insomnia, 15-21=clinical insomnia (moderate severity), and 22-28=clinical insomnia (severe).

    - Endpoints:
        - Change in ISI from Screening/Baseline Assessment to Prep Visit 2
        - Change in ISI from Screening/Baseline Assessment to Day A0 (immediately prior to psilocybin dosing)
        - Change in ISI from Screening/Baseline Assessment to Day A7
        - Change in ISI from Screening/Baseline Assessment to Day A14
        - Change in ISI from Screening/Baseline Assessment to Day A21

        If the participant remits at Day A21:
        - Change in ISI from Screening/Baseline Assessment to Day A90
        - Change in ISI from Screening/Baseline Assessment to Day A365

        If a second dose of psilocybin is required:
        - Change in ISI from Screening/Baseline Assessment to Day B0 (immediately prior to psilocybin dosing)
        - Change in ISI from Screening/Baseline Assessment to Day B7
        - Change in ISI from Screening/Baseline Assessment to Day B14
        - Change in ISI from Screening/Baseline Assessment to Day B21
        - Change in ISI from Screening/Baseline Assessment to Day B90
        - Change in ISI from Screening/Baseline Assessment to Day B365

4. Quality of life (participant-reported)

    - Measure: Quality of Life in Bipolar Disorder Questionnaire (QoL-BD full scale). The QoL-BD full scale is a 56-item questionnaire that measures 12 basic domains of quality of life and 2 optional domains. Each domain contains 4 items rated on a 5-point scale (1 “Strongly Disagree” to 5 “Strongly Agree). The total score ranges from 48-240 with higher scores indicating greater quality of life.

    - Endpoints
        - Change in QoL-Bipolar Disorder from Screening/Baseline Assessment to Day A21

        If the participant remits at Day A21:
        - Change in QoL-Bipolar Disorder from Screening/Baseline Assessment to Day A90
        - Change in QoL-Bipolar Disorder from Screening/Baseline Assessment to Day A365

        If a second dose of psilocybin is required:
        - Change in QoL-Bipolar Disorder from Screening/Baseline Assessment to Day B21
        - Change in QoL-Bipolar Disorder from Screening/Baseline Assessment to Day B90
        - Change in QoL-Bipolar Disorder from Screening/Baseline Assessment to Day B365

5. Treatment engagement (therapist-reported)

    - Measure: Engagement with Mental Health Services Scale (EMHSS). The EMHSS is a 11-item scale that measures 6 components of treatment engagement reported by the mental health therapist.

Each item is rated on a 5-point scale ranging from 1-5. The total score ranges from 11 (no engagement) to 55 (full engagement). Scores < 33 indicates progressively poor engagement, and scores ≥ 33 indicates progressively good engagement.

- Endpoints
    - Change in therapist-reported EMHSS from Screening/Baseline Assessment to Day A21

    If the participant remits at Day A21:
    - Change in therapist-reported EMHSS from Screening/Baseline Assessment to Day A90

    If a second dose of psilocybin is required:
    - Change in therapist-reported EMHSS from Screening/Baseline Assessment to Day B21
    - Change in Engagement Measure from Screening/Baseline Assessment to Day B90

6. Borderline personality disorder symptoms (clinician-reported)

- Measure: Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD). The ZAN-BPD is a 9-item scale used to assess the change in borderline psychopathy. Each item is rated on a 5-point scale from 0-4. The total score ranges from 0-36 with higher scores indicating greater severity in symptoms.

- Endpoint:

    If the participant remits at Day A21:
    - Change in ZAN-BPD from Screening/Baseline Assessment to Day A90
    - Change in ZAN-BPD from Screening/Baseline Assessment to Day A365

    If a second dose of psilocybin is required:
    - Change in ZAN-BPD from Screening/Baseline Assessment to Day B90
    - Change in ZAN-BPD from Screening/Baseline Assessment to Day B365

7. Adult attachment (participant-reported)

- Measure: Experiences in Close Relationships-Modified 16-Item Scale (ECR-M16). The 16-item Experiences in Close Relationships-Modified 16-Item Scale will be used to assess general adult attachment anxiety and attachment avoidance. Each scale has 8 items (range: 8-126) that are rated on a 7-point scale from 1 (Disagree) to 7 (Agree). Items are summed separately for each attachment dimension to calculate a continuous, overall attachment anxiety score and attachment avoidance score. Lower scores on each dimension of attachment anxiety and avoidance represent greater levels of attachment security.

- Endpoints
    - Change in ECR-M16 from Screening/Baseline Assessment to Day A21

    If the participant remits at Day A21:
    - Change in ECR-M16 from Screening/Baseline Assessment to Day A90
    - Change in ECR-M16 from Screening/Baseline Assessment to Day A365

    If a second dose of psilocybin is required:
    - Change in ECR-M16 from Screening/Baseline Assessment to Day B21
    - Change in ECR-M16 from Screening/Baseline Assessment to Day B90
    - Change in ECR-M16 from Screening/Baseline Assessment to Day B365

8. Recovery (participant-reported)

- Measure: The Bipolar Recovery Questionnaire (BRQ) assesses recovery experiences in individuals with a diagnosis of bipolar disorder. The self-report scale is 36 items long and assesses the degree to which the participant feels they have recovered from their bipolar illness.

- Endpoints:
    - Change in BRQ from Screening/Baseline Assessment to Day A21

    If the participant remits at Day A21:
    - Change in BRQ from Screening/Baseline Assessment to Day A90
    - Change in BRQ from Screening/Baseline Assessment to Day A365

    If a second dose of psilocybin is required:
    - Change in BRQ from Screening/Baseline Assessment to Day B21
    - Change in BRQ from Screening/Baseline Assessment to Day B90
    - Change in BRQ from Screening/Baseline Assessment to Day B365

9. Trauma-related symptoms (participant-reported)

- Measure: Adverse Childhood Experience (ACE) Questionnaire is a 10-item self-report measure assessing 10 types of childhood trauma. The measure helps identify participant's childhood abuse and neglect and family dysfunction, and to better understand their history of exposure to trauma.

    - This measure is used as part of the Screening/Baseline Assessment packet only.

- Measure: The PTSD Checklist for DSM-5 (PCL-5) is a is a 20-item self-report measure that assesses the 20 DSM-5 symptoms of PTSD. The PCL-5 has a variety of purposes, including monitoring symptom change during and after treatment, screening individuals for PTSD, and making a provisional PTSD. It can be completed in approximately 5-10 minutes.

- Endpoints:

    If the participant remits at Day A21:
    - Change in PCL-5 from Screening/Baseline Assessment to Day A90
    - Change in PCL-5 from Screening/Baseline Assessment to Day A365

    If a second dose of psilocybin is required:
    - Change in PCL-5 from Screening/Baseline Assessment to Day B90
    - Change in PCL-5 from Screening/Baseline Assessment to Day B365

10. Treatment Expectation

- Measure: Stanford Expectations of Treatment Scale (SETS) is an instrument for measuring positive and negative treatment expectancies.

- Endpoints:

    - Assessment at Screening/Baseline Visit

11. We will use six additional measures to quantify subjective effects of psilocybin:

- Subjective psychedelic intensity ratings will be measured using the Likert scale (0-10 rating scale, 0=not intense at all, 10= highest intensity imaginable), along with facilitator perceived rating of drug intensity, at 30, 60, 90, 120, 240, and 360 thereafter
- The Mystical Experiences Questionnaire (MEQ30), the Challenging Experiences Questionnaire (CEQ), Emotional Breakthrough Inventory (EBI) and the Psychological Insight Questionnaire (PIQ) will be used at the end of each psilocybin administration session (Day A0 and Day B0) to characterize participants' perspective on acute impacts of psilocybin treatment. Participants will also complete a post-dose journal the night following their dosing session prior to A1/B1 preparation session.
- The study-specific Transformational Experiences Questionnaire (TEQ) (participant-reported) will be used three weeks after the initial psilocybin session (Day A21) if the participant remitted at Day A21 or after three weeks (Day B21) if the second psilocybin dose was required to characterize participants' perspective on longer term impacts of psilocybin treatment.

12. Antidepressant Withdrawal

- Endpoints
    - Change in DESS from Screening/Baseline to Dose A
    - Change in DESS from Screening/Baseline to Dose B

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2 open-label, single-arm, single-site pilot study (N=14) of oral psilocybin (psilocybin 3-[2-(dimethylamino)ethyl]-1H-indol-4-yl] dihydrogen phosphate) treatment with an optional dose escalation for depression in people ages 30 to 65, who meet DSM-5 criteria for BD 2, who are also currently in a depressive episode and have a 22+ on the 10-item Montgomery-Asberg Depression (MADRS) Rating Scale (consistent with moderate or greater depressive symptom severity). The study is designed primarily to examine the safety, tolerability, and feasibility of psilocybin therapy in this patient population. Secondarily, the study is designed to generate preliminary evidence of psilocybin-induced improvement in depression and quality of life in BD 2.

As in previous clinical trials involving psychedelics, participants will complete significant preparation before psilocybin administration, will take psilocybin within a supportive clinical environment, and will complete multiple follow-up integration sessions to discuss their experience (Garcia-Romeu & Richards, 2018; Trope et al., 2019). This emphasis on context enhances participant safety and is considered best practice (Johnson et al., 2008). Participants will complete preparatory visits with trained at least one facilitator designed to provide information about the effects of psilocybin and to build rapport/trust. Following preparatory visits, participants will receive a low-moderate dose of 10mg oral psilocybin during a session supervised by the facilitator(s) and a physician who conduct safety monitoring throughout. Those who do not experience significant adverse events during or following the session and whose depression does not remit at three weeks after the initial dose (Day A21), will continue to a second psilocybin session. During the second session, participants will receive a moderate-high dose of 25mg oral. The second psilocybin session will involve the same structure, supervision, and monitoring as the first. Following psilocybin administration sessions, participants will complete integration sessions with the facilitator(s).

4.2 Scientific Rationale for Study Design

Though several trials of psilocybin therapy have been conducted in clinical populations such as patients with a terminal cancer diagnosis (Griffiths et al., 2016; Ross et al., 2016), treatment-resistant depression (Carhart-Harris et al., 2016), obsessive-compulsive disorder (Moreno et al., 2006), alcohol use disorder (Bogenschutz et al., 2015), and long-term AIDS survivors (Anderson et al., 2020), these previous trials have excluded participants with bipolar disorders. Thus, a critical first step in assessing the potential of psilocybin therapy for patients with BD 2 is to gather safety, tolerability, and feasibility data via an open-label pilot study.

4.3 Justification for Dose

4.3.1 Route of administration

Psilocybin is orally active and well-tolerated when administered by mouth. The onset of subjective effects is 20-40 minutes, effects peak after another 60-90min and last for another 60-120min (Hasler et al., 2004). All modern clinical trials administering psilocybin (Anderson et al., 2020; Bogenschutz et al., 2015; Carhart-Harris et al., 2016; Griffiths et al., 2016; Grob et al., 2011; Moreno et al., 2006; Ross et al., 2016) have used this route, and a recent positron emission tomography (PET) study demonstrated that oral administration leads to dose-dependent occupancy of 5-HT2A receptors (5-HTA receptor stimulation is associated with the subjective psychedelic experience and thought to be a key determinant in psychedelic-induced neural changes) (Madsen et al., 2019).

4.3.2 Dosages and Dosing Regimen

As examining safety and tolerability are primary objectives of this study, we will use a conservative dose-escalation protocol: a low-moderate dose of 10mg will be administered during the first session (Day A0). If this low-moderate dose is not associated with adverse events, mania or suicidality, and if depressive symptoms remit (≤6 on the MADRS) at Day A21, three weeks after the initial dose, it will be considered a positive treatment response and the second dose will not be given. If depressive symptoms remain (≥7 on the MADRS) at Day A21, three weeks after initial dosing, then a moderate-high dose of 25mg will be administered during a second session (Day B0). This protocol is designed to enhance participants' safety by allowing for detection of any adverse effects in response to 10mg before administering a higher dose. Also, we will minimize exposing participants to unnecessary risk by not escalating the dose if they have an adequate response to the low test dose.

Justification for the selected doses comes from prior work in healthy people as well as in clinical populations. The dose of a psychedelic is a reliable predictor of the nature of the subsequent psychological response (Griffiths et al., 2011; Nour et al., 2016; Studerus et al., 2011). A low dose (3–5 mg/70 kg) will likely yield a subjectively detectable sympathomimetic, but not hallucinogenic, effect (Passie et al., 2002). A 10mg dose (or similar) has been used in multiple previous studies in healthy people, leading to changes in mood and effects on processing of social information (Grimm et al., 2018; Preller et al., 2016) but an absence of hallucinogenic effects.

At higher doses (20-40 mg/70 kg), effects will become more profound as the functioning of higher levels of the global hierarchy become disrupted, potentially accounting for phenomena such as significant changes in sensory perception, the dissolution of ego boundaries and potential long-term changes in perspective (Carhart-Harris & Friston, 2019). Through multiple studies in healthy people, Griffiths et al. (2011) found that given the odds of attaining a complete mystical experience versus having a temporary anxiety reaction during the drug experience, the optimal dose likely falls between approximately 20-30 mg/70 kg. This dose range has been successfully used in multiple clinical trials thus far targeting depression in populations of people with terminal cancer diagnoses (Grob et al., 2011; Ross et al., 2016), alcohol use disorder (Bogenschutz et al., 2015), tobacco use disorder (Johnson et al., 2014), treatment-resistant depression (Carhart-Harris et al., 2016), long-term AIDS survivors (Anderson et al., 2020).

Though we expect that the high dose of 25mg will be required to improve depression, administering the 10mg dose will also allow us to observe whether people with BD 2 respond to a lower dose of psilocybin than observed thus far in other clinical populations. This is an important issue given the priority of minimizing medication burden for people with bipolar disorders.

Justification for fixed doses as opposed to a weight-based strategy comes from: 1) a previous clinical trial in people with treatment-resistant depression that used a fixed dose of 10mg followed by a fixed dose of 25mg one week later that significantly reduced depressive symptoms and reported no serious adverse events (Carhart-Harris et al., 2016); 2) a pharmacokinetic study that compared psilocin (the active metabolite of psilocybin) exposure from oral doses of psilocybin ranging 0.3-0.6 mg/kg and simulations for fixed 20 and 25mg doses, finding that a fixed dose of 25mg results in psilocin area under the concentration-time curve (AUC) and maximum concentration (Cmax) similar to those resulting from an individualized 0.3mg/kg dose (Brown et al., 2017). The same study suggests that dose adjustments are not necessary in people with mild to moderate renal impairment, as less than 5% of oral psilocybin was excreted in the urine as psilocin.

4.3.4 End of Study Definition

A participant is considered to have completed the study if they have completed all phases of the study including the final 3-month follow-up (See Section 1.3).

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Able to provide signed and dated informed consent form
2. Between 18-70 years old at the time of informed consent
3. Fluent in English
4. Must have had at least one unsuccessful medication trials for their bipolar depression (each lasting 6 weeks or more).
5. Must be on a consistent regimen of non-exclusionary psychiatric medications for last two months (Note: exclusionary medications removed as part of taper must be removed prior for a minimum of 5 half-lives)
6. Have no changes in medication or surgical procedures anticipated for trial duration
7. Commit to attend all study visits and participate in all remote data collection procedures
8. Current major depressive episode of ≥4 weeks duration as determined by the Structured Clinical Interview for the DSM-5 (SCID-5) and a minimum score of 19+ on the Montgomery-Asberg Depression Rating Scale (MADRS) at Screening/Baseline
9. Have an identified support person who is willing and able to serve in the role of observer/informant for data collection procedures.
10. Have a DSM-5 psychiatric diagnosis, as determined by the SCID-5 conducted during screening, of BD 2. DSM-5 requires a 4 consecutive day minimum to diagnose hypomania, but a 2-day minimum will be used as current data suggests the shortened criteria is more prevalent. Psychiatric diagnoses are determined by UCSF clinical staff.
11. For people of reproductive potential: agree to use highly effective contraception from entry into the trial through the end of the study (Day A90 or B90).
12. Agree that for one week preceding each psilocybin session, they will refrain from taking any nonprescription medication, nutritional supplement, or herbal supplement except when approved by the research team. Exceptions will be evaluated by the research team and will include acetaminophen, non-steroidal anti-inflammatory drugs, and common doses of vitamins and minerals.
13. Agree to abstain from inhaled nicotine containing products from 7 days before through 24 hours after each psilocybin administration.
14. Agree to consume approximately the same amount of caffeine-containing beverages (e.g., coffee, tea) that they usually consume before arriving at the research unit on the mornings of psilocybin administration sessions. If the participant does not routinely consume caffeinated beverages, they must agree not to do so prior to psilocybin administration sessions.

15. Agree not to use products or substances containing Δ^9-tetrahydrocannabinol (THC) for a at least 72 hours prior to each psilocybin administration session and 24 hours following each psilocybin administration session.

16. Agree not to use products or substances containing cannabidiol (CBD) for a minimum of 72 hours prior to each psilocybin administration session and 24 hours following each psilocybin administration session.

17. Agree not to consume alcoholic beverages for at least 24 hours prior to and 24 hours following each psilocybin administration session.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Current or history of meeting DSM-5 criteria for a bipolar disorder type 1

2. Current hypomania measured by SCID-5

3. Lifetime history of medication or drug induced mania, hypomania or psychosis as measured by SCID-5

4. Currently receiving electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS). Previous treatment with ECT and/or TMS is permitted; last treatment must be at least 30 days prior to entry into this trial.

5. Participation in a clinical trial within 30 days of entry into this trial or treatment with another investigational drug or other intervention within 30 days or 5 half-lives, whichever is longer, prior to entry into this trial or during the trial.

6. Pregnancy as indicated by a positive urine pregnancy test during screening, lactation, or the intention of becoming pregnant within 3 months of entry into this trial.

7. Current suicidality with intent or history of suicide attempt requiring hospitalization in the past year measured by C-SSRS.

8. Current severity of depression symptoms warranting immediate treatment as determined by the research team (e.g. due to elevated risk of harming self, elevated risk of harming others, or inability to provide for basic needs). UCSF clinical staff will assess these individuals, determine the appropriate level of care, and coordinate with the individuals' primary providers.

9. History of meeting DSM-5 criteria for a schizophrenia spectrum or other psychotic disorder

10. History of psychotic symptoms as determined by SCID-5. Exceptions will be made at the research team's discretion for psychotic symptoms experienced more than 2 years prior to entry into this trial.

11. Current or history within the last year of meeting DSM-5 criteria for a moderate or severe alcohol or drug use disorder, excluding caffeine.

12. Current psychiatric condition judged to be incompatible with establishment of rapport or safe exposure to psilocybin treatment procedures as determined by the investigators.

13. History of meeting DSM-5 criteria for either hallucinogen use disorder (moderate or severe) or hallucinogen persisting perception disorder (HPPD).

14. History of using any psychedelic substances including psilocybin, lysergic acid diethylamide (LSD), mescaline (and natural products containing mescaline including peyote and San Pedro cactus), N,N-Dimethyltryptamine (DMT), natural products containing DMT including ayahuasca and 5-Methoxy-N,N-dimethyltryptamine (5-MeO-DMT), ibogaine, 2C compounds, 3,4-methylenedioxy-methamphetamine (MDMA), or methylone within the past 6 months or as determined clinically significant by the principle investigator.

15. Cancer with known central nervous system (CNS) involvement, CNS infection, or other major CNS disease.

16. Epilepsy or other seizure disorder in adulthood.

17. Supplemental oxygen requirement.

18. Blood or needle phobia.

19. Allergy or intolerance to any of the materials contained in the drug product.

20. Renal insufficiency (creatinine clearance < 40 ml/min using Cockraft and Gault equation).

21. Poorly controlled diabetes mellitus (e.g. history of hypoglycemic episode or acute treatment for hyperglycemia on the current medication regimen).

22. Cardiovascular conditions:
    - Elevated blood pressure during enrollment phase or prior to dose administration as defined as:
        - Screening blood pressure SBP $\geq$135 mmHg or DBP $\geq$85 mmHg
        - Dosing day blood pressure SBP $\geq$ 140 mmHg or DBP $\geq$ 90mmHg
    - Tachycardia defined as heart rate (HR) >90 beats per minute taken during the screening period
    - Bradycardia (minimum acceptable heart rate at screening is 50 bpm unless the individual is cleared for participation by a cardiologist, in accordance with the American College of Cardiology's 2018 guidelines for bradycardia)
    - Angina
    - Clinically significant EKG abnormality (e.g. atrial fibrillation, QT/QTc>450 milliseconds)
    - Artificial heart valve
    - History of Transient Ischemic Attack (TIA) within last 6 months
    - History of stroke
    - History of peripheral or pulmonary vascular disease
    - Any other significant current or history of a cardiovascular condition that would preclude safe participation in the study based on the clinical judgment of the investigators

23. Hepatic dysfunction as indicated by any of the following values:
    - GGT > 3 x upper limit of normal
    - AST > 3 x upper limit of normal
    - ALT > 3 x upper limit of. normal
    - Total bilirubin > 3.0 mg/dl

24. Treatment with a drug that has hepatotoxic potential (e.g. tamoxifen) within 30 days of entry into this trial.

25. Use of any of the following concomitant medications or unwillingness or inability to discontinue according to medication taper including:
    - Antidepressants:
        - SSRIs
        - SNRIs
        - Tricyclic/Tetracyclic antidepressants
        - MAO inhibitors - participants must have discontinued 2 weeks prior to enrollment
        - other antidepressants including mirtazapine, nefazodone, trazodone, vilazodone, vortioxetine
        - (Bupropion allowed)
    - Other agents that may be associated with serotonin syndrome:
        - St. John's Wort
        - S-adenosyl-methionine (SAM-e)
        - 5-Hydroxytryptophan (5-HTP)
        - Dextromethorphan
        - Lithium
        - Linezolid
        - Buspirone
        - Lorcaserin
        - (Lamotrigine allowed)
        - (Gabapentin allowed)
        - (Pregabalin allowed)
    - Agents that may interact with psilocybin metabolism/effects:
        - Serotonin antagonists (e.g,. cyclobenzaprine, ondansetron)
        - Antipsychotics (PRN antipsychotic use is acceptable as long as the participant can abstain from use for at least 5 half-lives before each dosing session unless prescribed by study clinician)
        - Other dopamine antagonists (e.g., metoclopromide, promethazine, prochlorperazine)
        - Modulators of uridine diphosphate (UDP) or glucuronosyltransferase (UGT) (e.g., COMT inhibitors, valproate, diclofenac, mefenamic acid, verapamil, ketoconazole, itraconazole, probenecid, phenobarbital, protease inhibitors)
        - L-Methylfolate (>/= 7.5mg/day)
        - Esketamine and Ketamine
    - Agents that may increase the risk of psychotic symptoms:
        - Dopamine agonists (e.g. pramipexole, apomorphine)
        - Stimulants e.g. modafinil, methylphenidate, atomoxetine, amphetamine derivatives (Note: may be resumed at A1 and will be stopped again for a minimum of 5 half-lives prior to B0)
        - (Guanfacine allowed)
        - NMDAR antagonists (e.g. amantadine, memantine, ketamine)
26. A positive urine toxicology screen including amphetamines, benzodiazepines (unless currently prescribed), cocaine, and MDMA on the morning of either psilocybin administration session.

27. Febrile illness within 2 weeks of entry into the trial.

28. Other medical condition(s) or diagnosis, physical exam finding, EKG or laboratory abnormality that precludes participation in study procedures due to safety concerns at the discretion of the investigators.

5.3 Lifestyle Considerations

See inclusion/exclusion criteria.

5.4 Screen Failures

Screen failures are defined as participants deemed ineligible during the Enrollment Phase, as a result of assessments conducted on Screening/Baseline Visits. These participants may provide informed consent but are not subsequently entered in the study. Screen failures may fail to meet inclusion criteria and/or meet exclusion criteria or withdraw consent. Screen failures will be identified by: review of medical records, physical exams, laboratory tests, clinician assessments, and participant reports.

Individuals who at screening would be excluded for acute illness, or sub-optimal management of a chronic medical issue (e.g., hypertension) may be rescreened and considered for the study if, under the guidance of their primary care physician, they successfully recover from acute illness or optimize management of chronic medical issues such that they no longer meet the exclusion criteria. At the investigators' discretion, assessments may be repeated for confirmation of eligibility.

Individuals who at screening would be excluded for taking contraindicated medications/supplements but are otherwise eligible will enter a medication taper. Only participants who are willing and able to, will be tapered off of their exclusionary medication(s) under the supervision of the study medical providers.

If a potential participant is deemed ineligible at any time during the Enrollment Phase and therefore qualifies as a screen failure, a study staff member will notify the potential participant promptly and no further study visits will be conducted. All potential participants who initiate screening will be documented to ensure transparent reporting to meet Consolidated Standards of Reporting Trials (CONSORT) requirements. Documentation will include demographics, screen failure details, and any AEs.

5.4 Strategies for Recruitment and Retention

<u>Recruitment</u>

Potential subjects will be recruited through clinician and self-referral, as well as brochures and flyers placed at UCSF and throughout the Bay Area. Interested patients will fill out a pre-screening questionnaire and followed-up via phone/video by study staff.

<u>Screening</u>

Patients will be pre-screened via online survey and over the phone or in person by the study staff. Following pre-screening, eligible participants will be contacted by study staff for further screening.

Eligibility will be determined by a chart review when possible to verify eligibility and an initial phone/video/in person interview. Study staff will contact the patient with further information about the study, including sending a copy of the consent form for review prior to in-person consent.

Based on clinical and human subject protection considerations, a potential subject will, under no circumstance, be advised to taper their current medication regimen prior to the screening visit.

Those deemed eligible will be scheduled for a screening visit with one of the study staff. Study staff will obtain signed informed consent either through an IRB-approved electronic consent process, or in person from the potential participant before any further screening procedure is done. Once consent is obtained, study staff will assign the potential participant a unique enrollment number, and complete screening procedures including medical and psychiatric history, physical examination, and bloodwork (if no results available within the last 6 months).

Informed consent will be obtained prior to full evaluation of inclusion and exclusion criteria.

Retention

This study requires participation over at least a 4 month period. Study staff will enhance participant retention in the following ways:

- Compensation for each screening and assessment portion of the study completed
- Reminders for study appointments by phone call, text message, and/or email

We will provide compensation for the , screening/baseline (3-hr), post first dose assessments (at 1-week (2-hr), 2-weeks (2hr), and 3-week (2-hr)), post second dosing assessments (at 1-week (2-hr),2-weeks (2hr), and 3 week (2-hr) - for those who receive 2 doses), 3-month (2-hr) assessments, and 1-year (2-hr) assessments. Participants will be incentivized with a $100 bonus if they complete more than 80% of study assessments & return any study equipment. We estimate 42-72 hours to complete all the assessments and will provide an extra $74 for travel and parking. Therefore, participant payment may total $499 to $649.

Participants will be reimbursed via petty cash, check, gift card or Greenphire ClinCard Participants may be asked to provide your social security number, date of birth, and address in order to be paid for the study. This information is kept secure and used to identify participant for compensation purposes. Stipends over $600 in a single tax year will result in UCSF generating a 1099 form for each individual participant to report to the IRS as taxable income. Participants must give the researchers address and Social Security number for IRS reporting purposes.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The investigational drug to be used in this trial is psilocybin, currently a Schedule I controlled substance according to the Drug Enforcement Agency (DEA). The psilocybin used in this study is synthetically manufactured in a laboratory and meets quality specifications suitable for human research use. No mushrooms naturally containing psilocybin are used in the manufacturing process. The drug is encapsulated using a hydroxypropyl methylcellulose (HPMC) capsule. Information about the pharmacology and toxicology of psilocybin is included in the Investigator's Brochure (IB).

6.1.2 DOSING AND ADMINISTRATION

All participants will receive a low-moderate fixed dose of 10mg during the first session (Day A0). Each participant's response to the 10mg dose will be evaluated during the 3 week period between psilocybin sessions. If the participant's depression has remitted (≤ 6 on the MADRS) three weeks after dosing, the participant will not receive a second dose (i.e., will be considered 'remitted') and will be followed for the final 90 day assessment (A90). If the participant's depression did not remit 3 weeks after the initial 10mg dosage, the second psilocybin session with a moderate-high dose of 25mg will be administered Day B0.

If there is any indication from the included measures (of mania, depression, suicidality, or psychosis) that leads the study staff to suspect that the patient's condition is worsening, (receiving a score of 6 or greater on the CGI-I), the study staff will determine the best clinical course of action (e.g., involvement of the participants mental health professional, removal from any further dose (if one remains), or hospitalization.

All doses of psilocybin in this study will be administered orally, in the morning following a light meal.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

For the purposes of this study, psilocybin is available from the laboratory of Dr. Roland Griffiths at Johns Hopkins University (IND#133202) and from Usona Institute (Madison, WI).

PI, Dr. Josh Woolley, is responsible for study drug accountability, reconciliation, record maintenance, and final disposition records.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Psilocybin will be provided to UCSF in powder form, and the UCSF Investigational Drug Service of the UCSF Department of Pharmacy Services will encapsulate the drug. Capsules will contain 10mg and 25mg of psilocybin. Capsules are Size 2 hydroxypropyl methylcellulose (HPMC), white opaque in appearance. Each capsule will be provided in an HDPE bottle and labeled as required.

6.2.3 Product Storage and Stability

Bottles containing trial medications will be stored in the UCSF research pharmacy or other DEA-approved storage location at the study site.

Psilocybin will be stored at 15-30°C. The PI will confirm that appropriate temperature conditions have been maintained during transit for all supplies of study drug received. Any concerns must be reported and resolved before use of the study drug.

Psilocybin will be stored in a secure, environmentally controlled vault in the Investigational Drug Service at UCSF Medical Center

6.2.4 Preparation

Not applicable.

6.3 Measures to Minimize Bias: Randomization and Blinding

As this is an open-label pilot study with the primary objective of assessing safety, tolerability, and feasibility, all participants will complete the same procedures and we will not use randomization or blinding measures.

6.4 Study Intervention Compliance

Participants' adherence to the protocol will be tracked via encounter (study visit or phone check-in) and individual assessment logs in a secure trial database.

6.5 Concomitant Therapy

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be recorded in this study are concomitant prescription medications, over-the-counter medications and supplements.

All concomitant medications will be verified at all in-person study visits including the three-month follow-up assessment (Day A90 or B90; See Section 1.3 Schedule of Activities). Medication dosage, dosing regimen, and any changes in a participant's reported use of medication will be tracked. Use of concomitant medications that are not permitted (See Section 5.2 Exclusion Criteria) may either pose a safety risk via drug-drug interactions or interfere with psilocybin's effect on depressive and anxious symptoms.

Participants agree to stop their outside mental health care from the Prep Visits to A/B21. Participants are expected to resume outside mental health care after A/B21. Participants must provide contact information for their primary mental healthcare provider and signed consent to communications between them and the study team for continuity of care (and, optionally, for them to agree to provide collateral data via survey). Information on the specific type of any psychotherapy orientation (e.g., Cognitive-Behavioral, Dialectical Behavior Therapy, psychodynamic) will be requested from the mental health treatment provider.

Information on any concomitant therapies aside from medication (e.g., acupuncture, meditation) will also be collected and tracked throughout the study. Participants will be asked not to start new therapies or discontinue

therapies for a week before the first psilocybin session (Day A0) and one week following the last psilocybin session (Day B7).

Safety and tolerability endpoints (See Section 3.2.1) will include summary tables listing all concomitant medications and other therapies.

3.5.1 Rescue Medicine

The study site will supply rescue medications that may be administered by a study clinician during psilocybin administration sessions (Day A0, Day B0) at their medical discretion. The following rescue medications may be used in the unlikely event that a participant requires a pharmacologic intervention to manage elevated blood pressure, anxiety, psychosis, or allergic reactions:

1. Nitroglycerin
2. Clonidine
3. Diazepam
4. Risperidone
5. Labetalol

The date and time of rescue medication administration, reason for administration, as well as the name and dosage regimen of the rescue medication will be recorded on the Concomitant Medications Log.

Use of psychotropic medications (diazepam or risperidone) will be limited to this acute management and thus will not require participants to be excluded from the trial.

If a medical or psychiatric emergency arises that cannot be safely managed on the research unit using the rescue medications listed above, the study clinician will transport the participant to the UCSF Emergency Department (ED) or call the UCSF Hospital Code Service if necessary.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Given that this trial is a pilot study designed to assess safety, tolerability, and feasibility, there are no *a priori* halting rules. A Safety Monitoring Committee (SMC; see Section 10.1.6) will be informed of all adverse events and will evaluate their impact. Discontinuation of the study intervention will be at the discretion of the PI and/or SMC.

The Principal Investigator (PI) or a member of the study staff will also monitor all subjects for adverse effects throughout their participation in the study. This will include carrying out a clinical interview for adverse events at each visit which will consist of asking the subject whether they experienced any new symptoms or changes since the last visit. In addition, a series of safety assessments will be carried out and the findings reviewed by the PI and study staff. These safety assessments will include: the Columbia Suicide Severity Rating Scale (CSSRS) (Posner et al., 2011), vital signs (height, weight, blood pressure, and pulse), physical examination, Beta-HCG serum pregnancy test, urine drug screen, complete blood count with differential, electrolytes, comprehensive metabolic panel including liver function tests, thyroid function tests, urinalysis, CGI-I, and ECG.

Any indication from the included measures (of mania, depression, suicidality, or psychosis) that leads the study staff to suspect that the patient's condition is worsening, receiving a score of 6 or greater on the CGI-I. At this point the study staff will determine the best clinical course of action (e.g., involvement of the participants mental health professional, removal from any further dose (if one remains), or hospitalization.

In terms of monitoring for suicidality, subjects will be assessed at every visit with the Columbia Suicide Severity Rating Scale (CSSR-S). Subjects who answer "yes" to item 5 of the CSSR-S ("Active suicidal ideation with specific plan and intent") and are considered by clinical interview to be at risk are immediately removed from the study and appropriate intervention is implemented. In case of ambiguity regarding suicidal plans, the patient is removed from the study and provided appropriate treatment. Any subject with an increase in suicidality will undergo thorough assessment by the study staff who will determine the appropriate course of action including whether acute intervention is needed and whether it is in the best interests of the subject to continue in the study. Subjects for whom continued participation is deemed not to be in their best interest will be discontinued from the study.

The PI will follow all Adverse Events until resolution or they no longer believe that it is clinically significant. AEs ongoing at the time of the last dose of study drug will be followed up for as long as necessary to adequately evaluate the participant's safety, until they are resolved, or until it is determined by the PI or designated Co-Investigator not to be clinically significant.

In the event that the study intervention is discontinued, the study staff will continue follow-up procedures for all participants who completed at least one psilocybin session (Day A0 and/or Day B0) to capture any adverse events (AEs). Participants will be strongly encouraged to maintain contact throughout the full study period in order to ensure adequate collection of safety and tolerability data.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

7.2.1 PARTICIPANT WITHDRAWAL OR TREATMENT DISCONTINUATION

Participants can withdraw consent or terminate early from the study at any time at their request except during periods of acute psilocybin effects on Day A0 or on Day B0. If a participant withdraws, the investigators will make a concerted effort via multiple outreach attempts to determine the reason.

If any clinically significant finding is identified or any AE occurs on/following the first psilocybin session (Day A0), the investigators will report these and assess whether completion of the second psilocybin session (Day B0) is appropriate or whether a change in participant management is warranted. The decision to abstain from the second psilocybin session (treatment discontinuation) does not mean withdrawal from the study. The decision to complete versus abstain from the second psilocybin session will be made collaboratively between study clinicians and individual participants, who will determine the course of action that is in the best interest of a given participant. Even if the participant abstains from the second psilocybin session, all remaining study procedures, including all follow-up assessments, will be completed as indicated by the study protocol.

7.2.2 DISCONTINUATION OF PARTICIPANTS BY THE INVESTIGATORS

The investigators may discontinue a participant from the trial if, in their clinical judgment, continuation is no longer in the participant's best interest or if the participant is unable to complete procedures critical for safety or for the scientific integrity of the trial. If the investigators discontinue a participant from the trial, they will explain their reasoning to the participant. Reasons that the investigators may discontinue a participant from the study include, but are not limited to:

- A subject is assessed with a CGI-I score 6 or higher
- Pregnancy
- Significant study intervention non-adherence
- Occurrence of an adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- In the opinion of the PI or Co-I that it is in the participant's best interest to discontinue study procedures.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF).

7.2.3 REPLACEMENT OF PARTICIPANTS

Participants who provide informed consent, complete the Enrollment Phase and the Preparation Phase, but do not complete the first psilocybin session (Day A0) may be replaced. Participants who provide informed consent, complete the Enrollment Phase, Preparation Phase, and first psilocybin administration session and subsequently withdraw/are withdrawn or discontinued from the study will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if they fail to return for three scheduled visits and are unable to be contacted by the study staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The study staff will attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the study staff will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's study file.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study with a primary reason of 'lost to follow-up.'

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

The following sub-sections provide a sequential overview of study procedures, with specific assessments of safety, tolerability, feasibility, and efficacy listed at their corresponding time points. Further details of procedures will be specified in the Manual of Operating Procedures (MOP). The specific timing of all procedures and assessments to be conducted at each study encounter are captured in *Section 1.3: Schedule of Activities (SoA)*.

For participants who may withdraw early from the study and therefore not complete all of the following, we will adapt procedures to assess the rationale for withdrawal during their final encounter. For details, see Section 7: Study Intervention Discontinuation and Participant Discontinuation/Withdrawal.

Please note that licensed mental health providers in this study are defined as one of the following: psychiatrist, psychologist (holding a Ph.D. or Psy.D. degree), or facilitator (holding a RN, NP, MFT, LMFT, LPCC or LCSW degree).

To ensure consistency, the investigators will make every attempt to conduct assessments at approximately the same time of the day at each visit.

8.1.1 OUTLINE OF TRIAL PROCEDURES AND ASSESSMENTS

8.1.1.2 ENROLLMENT PHASE

PRE-SCREENER QUESTIONNAIRE AND PHONE SCREENING (REMOTE 30-60 MIN.)

Interested individuals will be provided with an internet link to a Pre-Screener Questionnaire designed to camouflage sensitive eligibility criteria and preserve the integrity of the study protocol. The survey begins with study information and a request for electronic consent to be pre-screened. The survey will then gather participant demographics, basic information on health history and behaviors, as well as other buffer, non-sensitive information (e.g. “How many siblings do you have?”) that will not be saved or included in the study dataset. Research coordinators will review incoming submissions and add those who may be eligible to the list of potential study participants.

Trained research assistants will pre-screen individuals on the list of potential participants over the phone, according to a standardized script that confirms and expands upon information already collected in the Pre-Screener Questionnaire. Potential participants meeting the initial eligibility criteria will be informed about the study procedures and time requirements associated with participating. Interested participants will schedule a medical exam session with a physician to further assess eligibility criteria, gather baseline health data, and provide informed consent.

- Screen for Eligibility Criteria
- SCID-5 overview psychosis/mania
- Demographic questionnaire (age, sex, contact information, ethnicity)
- Gather information about participant’s medical history, medical record, concomitant medications, and family history
- Participant-reported measures: QIDS-SR, ASRM-14, medication list

- Medical history screen

SCREENING/BASELINE VISITS (~7 HOURS)

The baseline assessment will be completed prior to the first preparation session

- Obtain Participant's Informed Consent
- Participant-reported measures: ISI, QoL-BD, DESS, ECR-M16, BRQ, PHQ-15, AAQ-II, CCFQ, FFMQ, STQ, PCL-5, ACE, participant treatment expectancy (SETS), Adler SES Ladder
- MADRS, YMS, C-SSRS, PANSS, QIDS-SR, SCID-5, CGI-I, and ZAN-BPD will all be conducted by a clinical assessor to determine the presence of psychiatric disorders and severity of depressive symptoms.
- Support Person Report (MDBI), Therapist-reported outcomes (modified ASRM-14 and PHQ-9), Therapist-reported treatment engagement
- Lab work: CBC, CMP, TSH, free T4, pregnancy test
- Physical exam, vital signs, & EKG
- During screening participant may be asked to start a video diary. They will complete short 2 minute entries 1-5 times per week for entirety of study participation
- Computer Tasks (participants may be asked to complete computerized task outlined below or other similar tasks)
    - REDCap
        - Alternative Uses Tasks (AUT)
        - Remote Associates Test (RAT)
    - Inquisit
        - Probabilistic Reversal Learning Task
        - Cognitive Flexibility Task
    - Brain HQ
        - Sound Sweeps

8.1.1.3 MEDICATION TAPER

Potential participants who meet all other entry criteria at Screening but who are taking exclusionary medications will be eligible for continuation in the study but will enter a medication taper during which current psychotropic medications will be withdrawn under the supervision of a study psychiatric medical provider. Participants will be eligible to continue to each dosing session a minimum of 5 half-lives following last dose of prohibited medications.

8.1.1.4 PREPARATION PHASE:

If facilitators, PI, or the study physician believe that a participant would benefit from further preparation prior to the dosing sessions to ensure safety, additional visits may be scheduled before the psilocybin administration session.

- Participants will abstain from outside therapy from the time of first preparation session to 30 days following final dose administration session. NOTE: Participants will be permitted to see outside psychiatrists for prescription refills

PREPARATION SESSION 1 (~2-3 HOURS)

- Medication review
- CGI-I will all be conducted by facilitator to determine the overall wellbeing of the participant
- Introduction to psilocybin-assisted therapy. The primary purpose of the first preparation session is to build trust and rapport with the study facilitator and provide additional information to the participant about the psilocybin dosing session, such as possible effects that may occur while under the influence of psilocybin and how the facilitator might support them during the session (e.g., guiding to the bathroom, reassurances). Participants will be asked about their life and health, and to begin thinking of an intention to set for the psilocybin treatment session.

PREPARATION SESSION 2 (~2-3 HOURS)

- MADRS, YMS, C-SSRS, PANSS, and medication review
- Participant-reported measure: ISI, QIDS-SR
- CGI-I will all be conducted by facilitator to determine the overall wellbeing of the participant
- Introduction to psilocybin-assisted therapy. The primary purpose of the second preparation session is to continue to build trust and rapport between the study facilitator and participant, to provide additional information about the possible effects that may occur during the psilocybin dosing session, and to set an intention for the psilocybin dosing session.

PREPARATION SESSION 3 (~2-3 HOURS)

- QIDS-SR, ISI, CGI-I, medication review
- Introduction to psilocybin-assisted therapy. The primary purpose of the third preparation session is to continue to build trust and rapport between the study facilitator and participant, to provide additional information about the possible effects that may occur during the psilocybin dosing session, and to set an intention for the psilocybin dosing session. This visit will occur in the research unit. Participants will be familiarized with the dosing session room, which includes aesthetically appealing décor and a couch where they will lie down during the drug session. During the in-person preparation session, the participants vitals will be taken to both acclimate participant to this process for dosing session and ensure new development of hypertension has not occurred.
- Day A-7 (completed 1-7 days prior to dose administration)
    - Computer tasks

8.1.1.5 PHASE A

DAY A0: FIRST PSILOCYBIN-ASSISTED THERAPY DOSING SESSION (~8 HOURS)

Participants will arrive at the UCSF facility around 8:00 am and leave their shoes, keys, wallet, and phones to the study facilitator for safekeeping until the end of the session that day. Then, participants will complete questions regarding their medication usage today and yesterday. Prior to dosing, participants will complete ASRM-14, QIDS-SR, DESS and ISI. Urine toxicology, pregnancy test and breathalyzer will be administered. Should a positive urine toxicology, pregnancy and/or breathalyzer result occur, participants will be informed of their positive result and immediately evaluated by the on-site study physician to assess their condition before they are permitted to leave the research unit. If the study physician feels that they may not be able to get home safely, they will continue to be monitored/observed on the research unit and/or brought to the UCSF Emergency Department if appropriate. In either case, study staff will contact their designated support person. Participants with a positive result will not be

able to continue with the drug administration session that day. They may be rescheduled at the discretion of the investigators.

CGI-I will all be conducted by a clinical assessor to determine the overall wellbeing of the participant.

Vital signs (heart rate and blood pressure) will be recorded for safety and possible adverse events at 10 minutes prior to psilocybin ingestion and 30, 60, 90, 120, 240, and 360 thereafter.

Ten mg of psilocybin, in a pill capsule, will be orally administered to the participant with a small glass of water. Within 30 minutes of ingesting the psilocybin, participants will be asked to lay down on the couch and put on eye shades and headphones with a preselected music playlist. Participants will also be instructed to direct their attention inwards, trust, let go, and be open to whatever arises during the session. At least one trained facilitator will be present with the participant for the whole duration of the psilocybin session, and will adhere to the safety guidelines outlined by Johnson et al. (2008). The facilitator(s) will assess for any AEs that may occur during the session. The facilitator(s) will complete the facilitator report following the administration session. If the participant reports challenging psychological experiences, such as anxiety, fear, or confusion, the facilitator(s) may provide verbal and/or non-verbal reassurances. If there is any concern for anxiety that is not responsive to reassurance or any serious concern of psychosis or psychological risk, the study physician will be called. All possible efforts will be taken to avoid using restraints of any kind (e.g., physical, chemical; See section 6.5.1 on rescue medication), while also maintaining the safety of the participant and facilitator(s). For this class of adverse events, rescue medications listed in Section 6.5.1 may be used at the study staff's discretion.

The study physician is responsible for the overall safety of the participant and oversees medical management of the participant if needed. While a medical emergency is highly unlikely given the screening process and previous evidence of psilocybin's safety and tolerability, the physician will be on-site, within 5 minutes (walking distance), for the first three hours of the dosing session or until after the peak experience has ended (base on facilitators' reports). If a clinical emergency occurs, the study physician will be contacted immediately by phone and will report to the dosing room to evaluate the participant and administer rescue medications and/or provide other appropriate medical care. The most likely adverse event is hypertensive urgency (See Table 8B). If blood pressure is above 180 systolic or 110 diastolic, or deemed to be unsafe, the study physician will be called, if not already in the room, and blood pressure will be continually monitored. Rescue medications are stored directly outside the dosing room to ensure that the study physician has immediate access, and anti-hypertensive medication might be given to acutely decrease blood pressure. If the patient is clinically suspected of being in hypertensive emergency with signs of end-organ damage (e.g., chest pain, shortness of breath), then anti-hypertensive medication will be given (See Section 6.5.1) and the study team will dial 911 and patient will be transported to the UCSF Emergency Department for further evaluation and treatment.

Following the effects of the psilocybin, participants will be instructed to complete a detailed account of their experience to discuss during their integration session the next day. The participant will also complete self-report intensity ratings throughout the dosing session as well as MEQ-30, CEQ, PIQ, post-dose journal and EBI once the drug effects have worn off.

After all assessments are complete, the facilitator will confirm that the participant is ready to safely leave the research unit. Specifically, the facilitator is required to sign off that the (1) the participant is alert and oriented to person, place, and time; (2) the participant does not report or exhibit confusion, anxiety, or other concerning symptoms; (3) vital signs are within safe parameters; (4) the participant has indicated that they feel safe and competent to leave. If the participants are considered medically and psychiatrically safe to leave the research unit, the will be able to leave the research unit using pre-arranged transportation (support person or ride-share

organized by the study team) to their home or local accommodation. Participants will not be permitted to drive themselves from the research unit

The study physician will remain on-call throughout the night as a resource for the participant if they have any questions or concerns.

DAY A1: INTEGRATION SESSION 1 (1-3 HOURS):

In the day after dosing, the participant will complete the first integration session with their facilitator(s). Participants will be asked and encouraged to share about their. A primary goal of all integration sessions is to help the participant make sense of their psilocybin experience and discuss ways to incorporate any lessons/insights during the session into one's everyday life.

All integration sessions will be audio and video recorded to ensure treatment fidelity and for subsequent behavioral analyses. Participants may request that recording be stopped temporarily to discuss highly personal material.

The following will be assessed during the first integration visit before discussing experience:

- YMS, C-SSRS, PANSS, CGI-I, vitals, adverse events assessment, and medication review

FOLLOW-UP VISITS

On days when there is no formal assessment during the two weeks after dosing, facilitators will have brief phone check-ins with the participant to ensure that they are not at heightened risk for manic or psychotic symptoms.

The following efficacy endpoints will also be measured at these follow-up assessments:

- Day A4 and A11 Remote Phone Call
  - ASRM-14, QIDS-SR, adverse events assessment, medication review, and check-in
- Day A7 Integration Session (1-3 hours)
  - MADRS, YMS, C-SSRS, PANSS, CGI-I, ISI, support person report (MDBI), adverse events assessment, and medication review
  - Computer tasks
  - Remote surveys PHQ-15, AAQ-II, CCFQ, FFMQ, STQ

DAY A14: ASSESSMENT SESSION (1-3 HOURS):

Participants will complete a series of assessments during this visit with the option of an integration session, if desired.

If an integration session is needed, participants will be asked and encouraged to share about their experience with the facilitator(s) and how it impacts their life. A primary goal of all integration sessions is to help the participant make sense of their psilocybin experience and discuss ways to incorporate any lessons/insights during the session into one's everyday life.

All integration sessions will be audio and video recorded to ensure treatment fidelity and for subsequent behavioral analyses. Participants may request that recording be stopped temporarily to discuss highly personal material.

The following efficacy endpoints will also be measured at this follow-up assessment:

- MADRS, YMS, C-SSRS, PANSS, CGI-I, ISI, adverse events assessment, medication review

DAY A21: ASSESSMENT SESSION (1-3 HOURS):

Participants will complete a series of assessments during this visit.

The following efficacy endpoints will also be measured at this follow-up assessment:

- MADRS, YMS, C-SSRS, BRQ, PANSS, ISI, QoL-BD, ECR-M16, TEQ, Support person report (MDBI), Therapist-reported outcomes (modified ASRM-14 and PHQ-9), Therapist-reported treatment engagement, adverse events assessment, medication review

DAY A26: INTEGRATION / PREPARATION SESSION (1-3 HOURS)

The A21 Assessments will be reviewed to determine if the A26 facilitator visit will serve as an integration and closure visit or if it will serve as a preparation for B0 dosing session.

If participants have remitted depressive symptoms (≤ 6 on MADRS) at Day A21 Assessment Session, they will proceed with completing the A26 visit as an integration and closure to A0 dosing session. They will be followed for the remainder of study period (~10 weeks), instead of receiving the second psilocybin dose, and assessed again 3 months after the initial 10mg psilocybin dose (Day A90).

During the integration session, participants will be asked and encouraged to share about their experience with the facilitator(s) and how it impacts their life. A primary goal of all integration sessions is to help the participant make sense of their psilocybin experience and discuss ways to incorporate any lessons/insights during the session into one's everyday life.

If after the 10mg initial psilocybin dose, participants do not have associated adverse events, but their depressive symptoms remain (> 6 on the MADRS), will progress to the second psilocybin administration on Day B0 (~Day A27) with a preparation phone call on Day A26. The A26 visit will be used to prepare the participant for their B0 dosing session.

Preparation for psilocybin-assisted therapy. The primary purpose of the preparation session is to continue to build trust and rapport between the study facilitator and participant, to provide additional information about the possible effects that may occur during the psilocybin high-dose session, and to set an intention for the psilocybin dosing session.

All integration sessions will be audio and video recorded to ensure treatment fidelity and for subsequent behavioral analyses. Participants may request that recording be stopped temporarily to discuss highly personal material.

The following efficacy endpoints will also be measured at this follow-up assessment:

- CGI-I, adverse events assessment, medication review

DAY A90- 3- MONTH FOLLOW-UP ASSESSMENTS (1-2 HOURS):

If the participant remits three weeks after the initial dose (Day A21), they will be followed for three months after receiving the 10mg psilocybin dose. On Day A90, the study staff will conduct a debriefing session and complete an exit interview with the participant.

The following efficacy endpoints will be measured at this follow-up assessment:

- MADRS, YMS, C-SSRS, PANSS, CGI-I, BRQ, QIDS-SR, ISI, QoL-BD, ZAN-BPD, ECR-M16, Support person report (MDBI), Therapist-reported outcomes (modified ASRM-14 and PHQ-9), Therapist-reported treatment engagement, and adverse event assessments
- Video and Audio recorded qualitative interview may be completed at A90 - topics and questions asked described in qualitative interview source document, exact questions and topics discussed will be tailored to the individual participant and their responses to questions. Additional similar and qualifying questions may be asked at discretion of the interviewer.

DAY A365- 1-YEAR FOLLOW-UP ASSESSMENTS (1-2 HOURS):

If the participant remits three weeks after the initial dose (Day A21), they will be followed for one year after receiving the 10mg psilocybin dose.

The following efficacy endpoints will be measured at this follow-up assessment:

- MADRS, YMS, C-SSRS, PANSS, CGI-I, PCL-5, BRQ, ISI, QoL-BD, ZAN-BPD, ECR-M16
- Video and Audio recorded qualitative interview may be completed at A90 - topics and questions asked described in qualitative interview source document, exact questions and topics discussed will be tailored to the individual participant and their responses to questions. Additional similar and qualifying questions may be asked at discretion of the interviewer.

8.1.1.6 PHASE B

DAY B0 (DAY A27)-SECOND PSILOCYBIN-ASSISTED THERAPY DOSING SESSION (~8 HOURS):

Participants who do not remit (> 6 on the MADRS) after the initial 10mg dose of psilocybin will continue with Phase B of this study.

The same procedures are followed as for Day B0 (First psilocybin-assisted therapy dosing session, except for the dosage of psilocybin for this visit will be 25mg.

INTEGRATION SESSIONS AND FOLLOW-UPS:

Once again, for integration sessions, participants will be asked and encouraged to share about their experience with the facilitator(s) and how it impacts their life. A primary goal of all integration sessions is to help the participant make sense of their psilocybin experience and discuss ways to incorporate any lessons/insights during the session into one's everyday life.

All integration sessions will be audio and video recorded to ensure treatment fidelity and for subsequent behavioral analyses. Participants may request that recording be stopped temporarily to discuss highly personal material.

On days when there is no formal assessment during the two weeks after dosing, study team will have brief phone check-ins with the participant to ensure that they are not at heightened risk for manic or psychotic symptoms.

The following efficacy endpoints will also be measured at these follow-up assessments:

- Day B1 Integration Visit
  - YMS, C-SSRS, PANSS, CGI-I, vitals, adverse event assessments, and medication review
- Day B4 and B11 Remote Phone Call
  - ASRM-14, QIDS-SR, medication review, adverse event assessments, and check-in
- Day B7 Integration Visit
  - MADRS, YMS, C-SSRS, PANSS, CGI-I, ISI, support person report, adverse event assessments, and medication review
  - Computer tasks
  - Remote surveys PHQ-15, AAQ-II, CCFQ, FFMQ, STQ
- Day B14 Assessment Visit
  - MADRS, YMS, C-SSRS, PANSS, CGI-I, ISI, adverse event assessments, and medication review
- Day B21 Integration Visit
  - MADRS, YMS, C-SSRS, BRQ, PANSS, CGI-I, ISI, QoL-BD, ECR-M16, TEQ, Support person report (MDBI), Therapist-reported outcomes (modified ASRM-14 and PHQ-9), Therapist-reported treatment engagement, adverse event assessments, and medication review

DAY B90 3-MONTH FOLLOW-UP ASSESSMENTS (1-2 HOURS):

Study staff will conduct a debriefing session and complete an exit interview with the participant.

The following efficacy endpoints will be measured at this follow-up assessment:

- MADRS, YMS, C-SSRS, PANSS, CGI-I, QIDS-SR, ISI, QoL, ZAN-BPD, ECR-M16, BRQ, Support person report (MDBI), Therapist-reported outcomes (modified ASRM-14 and PHQ-9), Therapist-reported treatment engagement, and adverse event assessments
- Video and Audio recorded qualitative interview may be completed at B90 - topics and questions asked described in qualitative interview source document, exact questions and topics discussed will be tailored to the individual participant and their responses to questions. Additional similar and qualifying questions may be asked at discretion of the interviewer.

DAY B365 1-YEAR FOLLOW-UP ASSESSMENTS (1-2 HOURS):

The following efficacy endpoints will be measured at this follow-up assessment:

- MADRS, YMS, C-SSRS, PANSS, CGI-I, PCL-5, BRQ, ISI, QoL-BD, ZAN-BPD, ECR-M16
- Video and Audio recorded qualitative interview may be completed at B90 - topics and questions asked described in qualitative interview source document, exact questions and topics discussed will be tailored to the individual participant and their responses to questions. Additional similar and qualifying questions may be asked at discretion of the interviewer.

8.2 SAFETY AND OTHER ASSESSMENTS

See Section 8.1 above for safety and other assessments.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

In this study, any change in clinical status that is considered clinically significant by the investigators is considered an AE. A study physician will evaluate all Aes and ensure appropriate documentation in the secure database.

Any medical condition that is present at the time that the participant is screened will be considered to be baseline and not reported as an AE. However, if a participant's condition deteriorates at any time during the study, we will record it as an AE.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

The PI, in collaboration with a study physician and the safety monitoring committee (SMC) will consider an AE or suspected AE "serious" if it results in any of the following outcomes, per 21 CFR 312.32 (a):

1. Death
2. Life-threatening event (defined as an event in which the participant is at risk of death at the time of the event; does not refer to an event that hypothetically might have caused death if it was more severe)
3. Inpatient hospitalization
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. Congenital anomaly/birth defect
6. Important medical events that may not result in death, be life-threatening, or require hospitalization but, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (Aes) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

The PI, in collaboration with a study physician and the SMC, will assess the relationship between each AE and the study intervention based on their temporal relationship and clinical judgment. The physician will specifically evaluate whether there is a reasonable possibility that the study drug or procedure caused the AE, considering each of the following: natural history of the participant's underlying Bipolar II Disorder, concurrent illness, concomitant therapy, study-related procedures, accidents, and other external factors.

The PI will be responsible for establishing a degree of certainty about causality using the categories below:

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

Josh Woolley, PI, will be responsible for determining whether an adverse event (AE) is expected or unexpected. Reference safety information in the IB will be used to determine expectedness, based on Aes previously observed in related studies. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

An AE will be considered "unexpected" if it is not documented in the IB or not not documented at the specificity or severity that has been observed.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

All study staff who interact with the participants will have a role in capturing potential AEs throughout the duration of the study, from the point of written informed consent through the final follow-up encounter (Day B90). At each study encounter, the staff member(s) conducting assessments will inquire about the occurrence of Aes since the last encounter. Details of procedures for solicitation and reporting of AEs will be included in the Manual of Procedures (MOP).

Under the supervision of the PI, study staff will document changes in the severity of each AE to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent will require documentation of onset and duration of each episode. The PI, in collaboration with a study physician and the SMC, will track outcome information for each AE until resolution or stabilization which may be after the final study encounter (Day B90) if warranted.

The PI is responsible for the appropriate medical management of all AEs and for the safety of participants. In case of an AE, the PI will collaborate with a study physician to initiate appropriate treatment based on clinical judgement. In collaboration with the SMC, the PI and study physician will determine whether to withdraw a participant from the study.

The PI will be responsible for recording all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation (Day B90).

8.3.4.1 SOLICITED ADVERSE EVENTS

Because our primary objective is to assess safety, tolerability, and feasibility of psilocybin therapy for depression associated with Bipolar II Disorder, our primary endpoints include assessments to solicit potential AEs via physical exams, vital sign monitoring, clinician-administered assessments, participant reports, facilitator reports, and caregiver/support person reports (see Section 3 Outcomes and Endpoints). We will specifically solicit the following AEs through these assessments:

1. Signs of physiological toxicity (elevated blood pressure or heart rate will only be reported as an AE should medication be needed)
2. Acute psychological distress
3. Headache
4. Nausea
5. Increase in Bipolar II Disorder symptom severity

6. Persistent perceptual effects/psychotic symptoms
7. Increase in caregiver/support person-reported distress
8. Suicidality

8.3.4.2 Unsolicited Adverse Events

To capture any unsolicited AEs, study staff will ask participants open-ended questions regarding their physical and mental health at each encounter: "Have you noticed anything different since you started the study?" During encounters following psilocybin administration sessions, staff will also ask: "Have you noticed anything different since the dosing session?" Staff will record any observed or participant-reported AEs throughout the study from the point of written informed consent to the final assessments point (Day B90).

8.3.5 Adverse Event Reporting

The PI will report any AE to the IRB within 5 days for internal (on-site) definitely, probably or possibly related AND serious or unexpected adverse events and within 10 days for external (off-site) adverse events.

The PI will report any AE to the IRB and enter the following information into the secure database within 10 days of becoming aware of the AE:

- Description
- Date of onset and resolution
- Severity
- Relatedness to study drug/procedures
- Action taken
- Outcome

If all information is not known at the time of initial reporting, the PI will still make an initial report. In the event there is a question as to whether the AE is serious, the SMC will review the information. New or updated information relevant to an AE or potential SAE will be recorded in the secure database within 24 hours of the PI being aware of the new information.

The PI will ensure that all AEs are coded according to the Medical Dictionary for Regulatory Activities (MedDRA), a clinically validated, standardized international medical terminology dictionary developed by the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.

Details of the AE reporting process including a description and flow chart of: 1) when AEs are reported to the SMC, IRB, FDA, and other regulatory bodies; 2) which study staff members are responsible for completing AE reports; and 3) who receives notification of AEs will be included in the study MOP.

8.3.6 Serious Adverse Event Reporting

The PI will ensure that any AE considered serious or which meets the definition of an SAE included in **Section 8.2.2, Definition of Serious Adverse Events** will be recorded on the SAE case report form (CRF) set in the secure database within 24 hours of identification.

In accordance with 21 CFR 312.32(c)(1), the PI will notify the FDA in an IND safety report of potential serious risks as soon as possible, but in no case later than 15 calendar days after the PI determines that the information qualifies for reporting. In each IND safety report, the PI will identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction and analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information. The PI will report any suspected adverse reaction that is both serious and unexpected. The PI will report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

A. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
B. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug
C. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

The PI will conduct supplemental measurements and/or evaluations as medically indicated or as requested by the SMC to elucidate the nature and/or causality of the SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. New or updated information relevant to a SAE will be recorded in the originally completed CRF and updated within 24 hours of the PI being aware of the new information.

The SMC will review all SAEs at the time they are reported and, in collaboration with the PI, will determine whether the SAE must be reported to FDA/regulatory authorities on an expedited basis.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the participant is stable.

If a participant dies during participation in the study or during a recognized follow-up period, the investigators will provide the Medical Monitor with a copy of a death certificate and any post-mortem findings.

The PI will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the investigator's initial receipt of the information. All other serious, related, and unexpected events will be reported within 15 calendar days.

In addition, the PI will notify FDA in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the PI determines that the information qualifies for reporting.

The PI will also submit safety reports as required by the UCSF IRB.

Details including a description and flow chart of 1) when AEs are reported to the SMC, IRB, FDA, and other regulatory bodies; 2) which study staff members are responsible for completing AE reports; 3) who receives notification of AEs will be included in the study MOP.

8.3.7 Reporting Events to Participants

Not applicable.

8.3.8 Events of Special Interest

Not applicable.

8.3.9 Reporting of Pregnancy

People who are pregnant or planning to become pregnant are excluded from this study during screening (See Section 5 Inclusion and Exclusion Criteria).

However, there is a policy in place should a participant become pregnant. Pregnancy, in and of itself, is not regarded as an AE. A confirmed pregnancy in a participant (by urine or blood test) will be reported in the data system within 24 hrs of the PI being aware of the pregnancy.

The pregnancy will be followed until an outcome is known. (i.e., spontaneous miscarriage, elective termination, normal birth). All live births must be followed for a minimum of 30 days or to the first well-baby visit. All reports of congenital abnormalities/birth defects and spontaneous abortions/miscarriages should be reported as an SAE for this study. Elective abortion procedures, without complications, will not be considered as AEs, but will be captured on a pregnancy outcome form.

8.4 Unanticipated Problems

8.4.1 Definition of Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Due to the limited data available involving Bipolar II Disorder and psilocybin, the PI will review with the SMC and IRB and make appropriate changes to the protocol as needed, including ending the study.

8.4.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the lead PI. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;

- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the SMC within 15 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the SMC within 2 weeks of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 1 month of the IRB's receipt of the report of the problem from the investigator.

8.4.3 Reporting Unanticipated Problems to Participants

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

For the primary endpoints, no formal null and alternative hypotheses are provided because the main objective of this open-label pilot study is to assess safety, tolerability, and feasibility of psilocybin therapy. Descriptive statistics, including means, standard deviations, effect sizes, and 95% confidence intervals for continuous variables and frequencies and percentages for categorical variables, will be used to describe participant characteristics and the primary outcomes. These statistics will be used to optimize the protocol, methods, procedure, and overall implementation of the treatment for a well-powered randomized controlled trial.

To explore preliminary treatment efficacy, we will describe changes from baseline to key time points on our exploratory efficacy outcome measures with descriptive statistics including means, standard deviations, effect sizes, and 95% confidence intervals.

Full details of statistical analysis will be provided in the statistical analysis plan (SAP).

9.2 Sample Size Determination

No sample size calculations were conducted because the primary aim of this study was to determine the feasibility of participant recruitment and retention and the acceptability of the treatment to inform a larger, subsequent randomized controlled trial (RCT). Power calculations for our exploratory efficacy measures are not indicated. Pilot studies are often used to estimate values that are then utilized in power calculations for larger trials. If this pilot yields promising results, these statistics will be used to optimize the protocol, methods, procedure, and overall implementation of the treatment for a larger, future RCT.

Given budgetary and time constraints, we aim to recruit 14 participants over a 24-month period.

9.3 Populations for Analyses

All participants who were administered the dose of psilocybin will be included in the analysis dataset. We will make every attempt to obtain as much data as possible (e.g., following up with participants to complete assessments), but we will not impute missing data points or carry any data points forward.

9.4 Statistical Analyses

9.4.1 General Approach

We will use descriptive statistics to assess each of the primary endpoints described in Section 3 Objective and Endpoints. We will use frequencies to assess safety, tolerability, and feasibility (e.g. incidence of adverse events, rate of participant recruitment and retention, completion of scheduled assessments, acceptability and satisfaction with the treatment).

We will use descriptive statistics including means, standard deviations, partial eta-squared effect sizes, and 95% confidence intervals to describe changes in the exploratory efficacy endpoints as outlined in Section 3 Objectives

and Endpoints. Given the small sample size and pilot nature of this study, we will conduct ANOVAs for exploratory purposes.

Following Assessment in Clinical Trials (IMMPACT) recommendations, we will evaluate our exploratory efficacy endpoints as follows:

- A 15% change in the primary efficacy outcome will be considered clinically unimportant
- A 15%–30% change will be considered minimally clinically important
- A 30%–50% change will be considered moderately clinically important
- A 50% change or greater will be considered substantially clinically important

Remission will be defined as a score ≤6 on the MADRS.

9.4.2 Analysis of the Primary Efficacy Endpoint(s)

Safety and Tolerability:

We will report summary statistics for all adverse events (AEs) including serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs). We will report the severity, frequency, and relationship of AEs to the study intervention organized by System Organ Class (SOC). For each AE, we will report:

- Start date
- Stop date
- Severity
- Relationship to study intervention
- Expectedness
- Outcome
- Duration

We will code all AEs using the Medical Dictionary for Regulatory Activities (MedDRA).

Feasibility:

We will use frequencies and percentages to assess recruitment and retention. To do this, we will track the number of interested participants, number of eligible participants after pre-screening and screening, reasons for ineligibility, the number of enrolled participants who withdraw before completing all study procedures, and the reasons for withdrawal. We will also compute the percentage of scheduled assessments completed in the given timeframe as an average from all participants who began/completed treatment to assess feasibility of study procedures.

Acceptability:

We will assess treatment acceptability and participant satisfaction with the study-specific Treatment Satisfaction Questionnaire (TSQ), reporting means, standard deviations, frequencies, and percentages.

Treatment acceptability and participant satisfaction:

Treatment acceptability and participant satisfaction will be assessed with the following questions: 1) How acceptable did you find this treatment?; 2) How satisfied are you with this treatment?; 3) Compared to other

pharmacological treatments for Bipolar II Disorder you have tried, how satisfied are you with this treatment?; 4) How useful/helpful did you find this treatment?; 5) How satisfied were you with the frequency of contact with the facilitator(s)?; 6) How satisfied were you with the length of this treatment program?. Each of these items will be rated on a 5/7-point scale with scale anchors that match the content of each question (e.g., 1 = Not at all acceptable, 5 = Extremely acceptable). The target for treatment acceptability and participant satisfaction at each timepoint is ≥ 80%. The following open-ended questions will be used to gather additional information: 1) What were the benefits to this treatment for you?; 2) What were the challenges to participating in this study for you?; 3) Are there any changes you have noticed in yourself?; 4) Were there any changes you would suggest to the treatment program?. Quantitative and qualitative feedback regarding participant's experiences of the treatment will inform potential alterations in the study methods or procedures for larger RCTs.

Primary Endpoint from Secondary Objective: The primary endpoint for preliminary efficacy is change in depression symptoms, using the MADRS, from baseline to the 3-week follow-up. A paired-sample *t*-test will be used to test for significant improvements in mean scores of depressive symptoms at 3-week, compared to baseline, and these results will be presented as a Cohen's d effect size with a 95% CI. The population for these analyses is everyone who was administered psilocybin. Given this is a pilot study with the primary objective of examining feasibility, missing data will not be imputed. Outliers will be windsorized or handled with nonparametric transformations.

9.4.3 Analysis of the Secondary Endpoint(s)

We will assess each secondary (exploratory) endpoint as specified in Section 3: Outcomes and Endpoints. For each of the measures, we will report results using descriptive statistics and an effect size (partial eta-squared) with a 95% confidence interval. We will use a series of ANOVAs to explore changes in mean scores for each endpoint at key intervals as specified in Section 3. We will not impute missing data.

9.4.4 Safety Analyses

Safety analyses will include rates of serious adverse events that will be described with descriptive statistics. Safety will also be assessed during the psilocybin session by monitoring vital signs for tachycardia (HR>100bpm), bradycardia (HR<60bpm), hypertension (SBP>140mmHg or DBP>90mmHg) and hypotension (SBP<100mmHg or DBP<60mmHg).

9.4.5 Baseline Descriptive Statistics

Baseline characteristics and demographics will be presented with descriptive statistics (e.g., means, SDs, frequencies, percentages). Inferential statistics will not be used on baseline data because there is only one group in this study.

9.4.6 Planned Interim Analyses

We do not plan to conduct formal interim analyses given that this is a pilot trial. However, any concerning safety and tolerability finding in a study participant, including any SAE, will prompt an interim review of all safety data by the Safety Monitoring Committee (SMC). Enrollment and administration of the study drug will be suspended until the safety review is completed.

9.4.7 Sub-Group Analyses

No sub-group analyses are planned.

9.4.8 Tabulation of Individual participant Data

Individual participant data will be listed at each time point to better understand idiographic/within-person changes over time.

9.4.9 Exploratory Analyses

Exploratory analyses will examine whether participant experiences during the psilocybin-assisted therapy session predict changes in efficacy outcome measures. Specifically, the intensity of mystical experiences and psychological insight is expected to predict changes in psychological flexibility which is expected to predict pre-post treatment changes in secondary endpoints. We will explore whether the number of adverse childhood experiences moderate changes in efficacy endpoints following psilocybin-assisted therapy.

All efficacy analyses in this study are exploratory. We will use ANOVAs to examine depression, anxiety, and related function/quality of life measures following psilocybin therapy compared to baseline; specific endpoints are as described in Section 3: Outcomes and Endpoints.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

The process of obtaining and documenting informed consent in this study will comply with applicable regulatory requirements and adhere to ICH GCP. Prior to the beginning of the trial, the PI will have the IRB's written approval for the protocol and the written informed consent forms.

We are submitting the following consent materials, describing the study intervention, procedures, and risks, with this protocol:

- Pre-Screener Questionnaire Electronic Consent Form
- Phone Screen Verbal Consent Form
- Informed Consent Form
- Recruitment materials
- Consent for release of information (ROI) to Mental Healthcare Provider

10.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to an individual agreeing to participate in the study and continues throughout the individual's study participation. Consent forms used in this trial will be IRB-approved and the participant will be asked to read and review the documentation. Trained study staff will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants.

Participants will provide electronic informed consent for the Pre-Screener Questionnaire and verbal informed consent to participate in the Phone Screen.

Participants will provide written informed consent at the Screening/Baseline Assessment Visit. They will have the opportunity to carefully review the written consent form and ask questions prior to signing. Each participant will have the opportunity to discuss the study with their caregiver/support person and think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures that are included in the Screening/Baseline Assessment Visit.

Participants will also be asked to provide contact information for their primary mental healthcare provider, and to consent to study clinicians contacting them for purposes of continuation of care and safety. The participant will be given a copy of the informational letter for their mental healthcare provider of their signed consent for release of information.

We will protect the rights and welfare of participants by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. Study staff will also emphasize that

participants may withdraw from the study at any time, without prejudice. Each participant will receive a copy of the informed consent document for their records.

10.1.3 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated by the PI or by regulatory or other oversight bodies if there is sufficient reasonable cause. The suspending or termination party will provide written notification, documenting the reason for study suspension or termination to the study participants, funder, the Investigational New Drug (IND) sponsor, and regulatory authorities. The PI will promptly inform study participants and the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed per the requirements of the IRB and FDA.

For details on handling of enrolled study participants in the case of study termination, see **Section 7: Study Intervention Discontinuation and Participant Discontinuation/Withdrawal**.

10.1.4 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the investigators and other study staff. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the PI.

All research activities will be conducted in as private a setting as possible.

The SMC, IRB and other regulatory agencies, and the pharmaceutical company supplying study products may inspect all documents and records required to be maintained by the PI, including but not limited to, medical records and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Participants' contact information will be securely stored on-site in a password-protected database for internal use during the study. At the end of the study, all records will continue to be kept in the secure database for as long a period as dictated by the reviewing IRB.

All participants will be assigned a unique study identification code to allow for data to be entered and stored in de-identified forms whenever possible. All study data entry and study management systems used in this study will be secure and password protected.

Certificate of Confidentiality:

To further protect the privacy of study participants, we will obtain a Certificate of Confidentiality from the National Institutes of Health (NIH). This certificate allows the PI and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting the investigators and institution from being compelled to disclose information that would identify research participants, we expect that the Certificates of Confidentiality will help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.5 Future Use of Stored Specimens and Data

We will analyze and store data collected during this study at UCSF in accordance with IRB regulations. After the study is completed, data will be shared via secure, approved methods with collaborating researchers including those outside of the study team who have a role in data analysis. Whenever possible, data shared with collaborating researchers will be de-identified. Permission to transmit data to collaborating researchers for this purpose will be included in the informed consent.

10.1.6 Key Roles and Study Governance

The leadership committee is comprised of three PIs: Josh Woolley, MD/PhD, from University of California, San Francisco, David Gard, PhD, from San Francisco State University, and Ellen Bradley, MD, from University of California, San Francisco. Details of specific study team member roles and responsibilities will be included in the MOP.

10.1.7 Safety Oversight

Independent oversight is essential to ensure participants' protection and data integrity. In this trial, safety oversight will be under the direction of a Safety Monitoring Committee (SMC) composed of individuals with expertise in psychiatry, neurology, pharmacology, and patient advocacy. Members of the SMC are independent from study conduct and free of conflicts of interest. The SMC will meet at least semiannually for interim data review in addition to ad hoc meetings. The SMC will provide its input to the PI and to the IRB.

10.1.8 Clinical Monitoring

Clinical site monitoring ensures that the rights and well-being of participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirements.

Monitoring for this single-site trial will be performed throughout the study's duration by the SMC. Monitoring will include safety and tolerability data verification, and reports will be distributed to the IRB.

10.1.9 Quality Assurance and Quality Control

We will perform internal quality management on-site, which encompasses:

- Quality assurance (QA): measures to ensure that the trial is performed and the data are generated, documented, and reported in compliance with ICH GCP and the applicable regulatory requirement(s) such as Good Laboratory Practices (GLP) and Good Manufacturing Practices (GMP); (ICH E6 Section 1.46).
- Quality control (QC): operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled; (ICH E6 Section 1.47).

The study team will conduct these processes following written Standard Operating Procedures (SOPs) that describe documentation to be reviewed, frequency of review, and who is responsible for each step in this process. SOPs will also describe who is responsible for addressing any QA issues (e.g., correcting procedures that are not in compliance with protocol) and QC issues (e.g., correcting errors in data entry) that arise.

The PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of review by the SMC and inspection by local and regulatory authorities.

10.1.10 Data Handling and Record Keeping

10.1.10.1 Data Collection and Management Responsibilities

All data will be collected on-site by study staff members under the supervision of the PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Detailed descriptions of source documentation, CRFs, instructions for completing forms, data handling procedures, and data monitoring procedures will be described in the study MOP.

Study staff will enter clinical data, including adverse events (AEs), concomitant medications, and expected adverse reactions data, as well as clinical laboratory data into the secure electronic database. The electronic database system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Study staff will enter clinical data directly from the source documents.

10.1.10.2 Study Records Retention

We will retain study documents for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations or the IND sponsor's agreement.

10.1.11 Protocol Deviations

A protocol deviation is any noncompliance with the trial protocol, ICH GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the PI, or the study staff. As a result of deviations, the PI ensures that corrective actions are implemented promptly.

These practices are consistent with ICH GCP:

- Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3

- Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

The PI is responsible for maintaining continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity.

The PI will send all deviations to the reviewing IRB per their policies. The PI is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the process of handling protocol deviations will be included in the MOP.

10.1.12 Publication and Data Sharing Policy

This study will comply with the Clinical Trials Registration and Results Information Submission rule. As such, we will register the trial at ClinicalTrials.gov and submit results information to ClinicalTrials.gov.

We will make every attempt to disseminate results via publication in peer-reviewed journals. We will add final peer-reviewed journal manuscripts to the digital archive PubMed Central upon acceptance for publication to ensure access to our findings.

10.1.12 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. We will disclose and manage any conflict of interest of individuals who have a role in the design, conduct, analysis, publication, or any other aspect of this trial.

Individuals who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The PI is responsible for ensuring consistent policies and procedures for disclosure of all conflicts of interest and establishing a mechanism for the management of all reported dualities of interest.

10.2 Additional Considerations

Not applicable.

10.3 Abbreviations

ACE	Adverse Childhood Experience Questionnaire
AE	Adverse Event
ANCOVA	Analysis of Covariance
ASRM-14	Altman Self-Rating Mania Scale
BP 1 (BP I)	Bipolar 1 Disorder
BD 2 (BP II)	Bipolar 2 Disorder
BRQ	Bipolar Recovery Questionnaire
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression-Improvement Scale

CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CNS	Central Nervous System
CoC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
ECR-M16	Experiences in Close Relationships-Modified 16-Item
eCRF	Electronic Case Report Forms
EKG/ECG	Electrocardiogram
EMHSS	Engagement with Mental Health Services Scale
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
MADRS	Montgomery-Asberg Depression Rating Scale
HIPAA	Health Insurance Portability and Accountability Act
HPA	Hypothalamic-Pituitary-Adrenal
HPPD	Hallucinogen Persistent Perception Disorder
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISI	Insomnia Severity Index
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MDBI	Mood Disorder Burden Interview
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health

NIH IC	NIH Institute or Center
OCD	Obsessive-Compulsive Disorder
OHRP	Office for Human Research Protections
PANSS	Positive and Negative Syndrome Scale
PCL-5	PTSD Checklist for DSM-5
PI	Principal Investigator
PNS	Peripheral Nervous System
QA	Quality Assurance
QC	Quality Control
QIDS-SR	Quick Inventory of Depressive Symptomatology-Self-Report
QoL-BD	Quality of Life in Bipolar Disorder Questionnaire
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCID-5	The Structured Clinical Interview for the DSM-5
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Events
TEQ	Transformational Experiences Questionnaire
TRD	Treatment-Resistant Depression
TSH	Thyroid-Stimulating Hormone
TSQ-P	Treatment Satisfaction Questionnaire - Participant
TSQ-S	Treatment Satisfaction Questionnaire - Support Person
UCSF	University of California, San Francisco
UP	Unanticipated Problem
US	United States
YMS	Young Mania Scale
ZAN-BPD	Zanarini Rating Scale for Borderline Personality Disorder
MEQ-30	Mystical Experiences Questionnaire
CEQ	Challenging Experiences Questionnaire
PIQ	Psychological Insight Questionnaire
EBI	Emotional Breakthrough Inventory

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APPENDICES:

Scales/Measures:

1. Treatment Satisfaction Questionnaire – Participant (TSQ-P)

   [All rated on Likert 1-7]

1) How satisfied are you with the treatment that you received in this study?

2) How beneficial do you think the treatment has been for your health?

3) How harmful do you think the treatment has been for your health?

4) How much would you recommend this treatment to a close friend, family member, or loved one with health concerns similar to yours?

5) Open-ended: additional feedback

2. Treatment Satisfaction Questionnaire – Caregiver/Important Other (TSQ-C)

[All rated on Likert 1-7]

1) How satisfied are you with the treatment that X received in this study?

2) How beneficial do you think the treatment has been for X's health?

3) How harmful do you think the treatment has been for X's health?

4) How much would you recommend this treatment to a close friend, family member, or loved one with health concerns similar to X's?

5) Open-ended: additional feedback

3. TEQ:

- Did the experience significantly change your perspective on things that are important to you? (Likert 1-7)
    - if YES, qualitative elaboration
- How personally meaningful was the experience (from Griffiths 2006) Likert 1-7